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(AN/JOHNSON OR AN/ORTHO-MCNEIL): 5024 patents.
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Next 50 Hits

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Refine Search an/JOHNSON or an/ORTHO-MCNEIL

	PAT. NO.	Title
1	7,032,872	Universal laptop computer mount
2	7,032,831	Container for a device for dispensing a volatile liquid
3	D519,368	Swivel slider body with handle
4	7,031,880	Method and apparatus for assessing performance of an environmental control system
5	7,030,110	Cyclic oxyguanidine pyrazinones as protease inhibitors
6	7,030,095	Pediculicidal and ovacidal treatment compositions and methods for killing head lice and their eggs
7	7,029,654	Heteroaryl aminoguanidines and alkoxyguanidines and their use as protease inhibitors
8	7,029,049	Adjustable armrest
9	7,028,866	Pressurized plastic bottle for dispensing an aerosol
10	7,028,756	Apparatus for increasing a transfer of thermal energy through an inner surface of a hollow cylindrical dryer of a papermaking machine
11	7,028,405	Vibratory shaver
12	D518,883	Active material cartridge
13	7,026,132	Method of monitoring the effect of Cathepsin S inhibitors
14	7,026,034	Processing substrate and method of manufacturing same
15	7,025,951	Compositions and methods for darkening the skin
16	7,025,328	Damper actuator system
17	7,024,781	Vial illumination feature for a tool such as a level
18	D518,408	Decorative tower object having a tapered inner cavity
19	7,024,336	Method of and apparatus for evaluating the performance of a control system

20 7,024,254 T Method for controlling a discrete system
21 7,023,519 T Internal heater embedded in an LCD cell
22 7,022,395 T Disposable cutting sheet
23 7,021,494 T Automated cleansing sprayer having separate cleanser and air vent paths from bottle
24 7,021,009 T Emergency housing
25 D518,161 T Cover for volatile dispenser
26 7,018,797 T Method for treating neurodegenerative disorders
27 7,017,829 T Atomizer wicking system
28 7,017,775 T Container lid including venting and denesting features, and container having such a lid
29 7,017,772 T Pressure container
30 D517,322 T Threaded storage container lid
31 7,015,672 T Method for controlling a variable-reluctance machine
32 7,014,898 T Oxygen scavenging
33 7,014,127 T Aerosol dispenser assembly having low volatile organic compound (VOC) content
34 D516,859 T Tab for a container lid
35 7,011,615 T Method for making a multicompartment thermoplastic bag
36 7,011,425 T Luminary product
37 7,011,228 T Sealable container cover
38 7,010,530 T Event management system
39 7,010,087 T Density measurement method and apparatus therefor
40 7,009,519 T Product dispensing controlled by RFID tags
41 7,008,627 T Use of complexes for the preparation of compositions for the treatment of sensitive skin, preparation process and hypoallergenic compositions
42 7,008,620 T Depilatory compositions and articles and the use thereof
43 7,008,392 T Hemostatic cleansing swab
44 7,007,863 T Wick-based delivery system with wick made of different composite materials
45 7,007,861 T Methods and personal protection devices for repelling insects
46 7,004,804 T Trolling motor mount
47 7,004,509 T Journal bearing mounted hub seal rotary joint
48 D515,438 T Container
49 7,001,898 T Nonpeptide substituted spirobenzoazepines as vasopressin antagonists
50 7,001,773 T Artificial testing soil and method of testing

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Results of Search in US Patent Collection db for:
((AN/JOHNSON OR AN/ORTHO-MCNEIL) AND steroid): 42 patents.
Hits 1 through 42 out of 42

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Refine Search an/JOHNSON or an/ORTHO-MCNEIL and steroid

	PAT. NO.	Title
1	7,025,951	Compositions and methods for darkening the skin
2	6,986,747	Method of measuring the stress or relaxation level of a mammal
3	6,926,886	Compositions for darkening the skin and/or hair
4	6,881,756	Method for treating skin disorders
5	6,858,621	2-(quinolonyl)-fused heterocycles as androgen receptor modulators
6	6,830,755	Method for relaxing human beings using personal care compositions
7	6,797,697	Composition containing a peptide and a pigment and the use thereof in darkening the skin
8	6,765,011	7-heterocyclyl quinoline and thieno[2,3-b]pyridine derivatives useful as antagonists of gonadotropin releasing hormone
9	6,750,229	Methods for treating skin pigmentation
10	6,747,019	Low dose estrogen interrupted hormone replacement therapy
11	6,590,119	Methods for the synthesis of dioxoalkanoic acid compounds
12	6,583,179	Substituted aminoalkylamide derivatives as antagonists of follicle stimulating hormone
13	6,583,167	Methods and kits for treating and diagnosing leiomyomas
14	6,583,153	7-heterocyclyl quinoline and thieno[2,3-b]yridine derivatives useful as antagonists of gonadotropin releasing hormone
15	6,506,742	Soluble contraceptive liquid formulation
16	6,410,062	Method for the topical treatment and prevention of inflammatory disorders and related conditions using extracts of feverfew (Tanacetum parthenium)
17	6,407,056	Methods for altering hair growth and hair pigmentation by apoptosis in the follicular papillae and compositions therefor
18	6,323,219	Methods for treating immunomediated inflammatory disorders

19 6,238,683 Anhydrous topical skin preparations
20 6,225,525 T ATP-binding cassette transporter (ABC1) modified transgenic mice
21 6,214,815 T Triphasic oral contraceptive
22 6,149,935 T Solid matrix system for transdermal drug delivery
23 6,071,531 T Transdermal patch and method for administering 17-deacetyl norgestimate alone or in combination with an estrogen
24 5,993,787 T Composition base for topical therapeutic and cosmetic preparations
25 5,912,114 T Wound diagnosis by quantitating cortisol in wound fluids
26 5,723,144 T Ointment for wound treatment
27 5,693,624 T Sterile gel compositions for wound treatment
28 5,688,522 T Ointment for wound treatment
29 5,652,346 T Dicarboxylic acid oxidation products
30 4,579,844 T Topical anti-inflammatory drug therapy
31 4,473,565 T Topical anti-inflammatory drug therapy
32 4,372,887 T Iminopyrrolidinylindoles
33 4,370,321 T Progestational adjuvant therapy
34 4,360,518 T Topical anti-inflammatory drug therapy
35 4,282,216 T Topical anti-inflammatory drug therapy
36 4,259,238 T N-Phenyl amidines
37 4,196,212 T N-phenyl amidines
38 4,185,100 T Topical anti-inflammatory drug therapy
39 4,073,291 T Topical device for administering tretinoin
40 4,072,675 T N-phenyl amidines
41 4,049,714 T N-phenyl amidines
42 4,000,304 T Diuretic antiturombogenic and antiarrhythmic processes using N-substituted indole dimers and pyrrolobenzodia-zepine rearrangement products thereof

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Results of Search in US Patent Collection db for:
(((AN/JOHNSON OR AN/ORTHO-MCNEIL) AND steroid) AND norgestimate): 4 patents.
Hits 1 through 4 out of 4

Jump To

Refine Search an/JOHNSON or an/ORTHO-MCNEIL and steroid an

	PAT. NO.		Title
1	6,747,019	T	Low dose estrogen interrupted hormone replacement therapy
2	6,506,742	T	Soluble contraceptive liquid formulation
3	6,214,815	T	Triphasic oral contraceptive
4	6,071,531	T	Transdermal patch and method for administering 17-deacetyl norgestimate alone or in combination with an estrogen

USPTO Patent Full-Text and Image Database

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Results of Search in US Patent Collection db for:
(((AN/JOHNSON OR AN/ORTHO-MCNEIL) AND steroid) AND ((amorphous OR crystalline) OR non-crystalline)): 11 patents.
Hits 1 through 11 out of 11

Jump To

Refine Search an/JOHNSON or an/ORTHO-MCNEIL and steroid an

	PAT. NO.	Title
1	6,765,011	7-heterocyclyl quinoline and thieno[2,3-b]pyridine derivatives useful as antagonists of gonadotropin releasing hormone
2	6,583,179	Substituted aminoalkylamide derivatives as antagonists of follicle stimulating hormone
3	6,583,153	7-heterocyclyl quinoline and thieno[2,3-b]yridine derivatives useful as antagonists of gonadotropin releasing hormone
4	6,149,935	Solid matrix system for transdermal drug delivery
5	5,993,787	Composition base for topical therapeutic and cosmetic preparations
6	4,372,887	Iminopyrrolidinylindoles
7	4,259,238	N-Phenyl amidines
8	4,196,212	N-phenyl amidines
9	4,072,675	N-phenyl amidines
10	4,049,714	N-phenyl amidines
11	4,000,304	Diuretic antiturombogenic and antiarrhythmic processes using N-substituted indole dimers and pyrrolobenzodia-zepine rearrangement products thereof

USPTO PATENT FULL-TEXT AND IMAGE DATABASE

Searching US Patent Collection...

Results of Search in US Patent Collection db for:
(steroid AND ((amorphous OR crystalline) OR non-crystalline)): 3839 patents.
Hits 1 through 50 out of 3839

Next 50 Hits

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Refine Search steroid and (amorphous or crystalline or non-crystalli

	PAT. NO.	Title
1	7,034,182	Compounds to treat Alzheimer's disease
2	7,034,151	Process for preparing pyrrolotriazine kinase inhibitors
3	7,034,057	Compounds for the treatment of inflammatory disorders
4	7,033,781	Whole cell engineering by mutagenizing a substantial portion of a starting genome, combining mutations, and optionally repeating
5	7,033,621	Isoflavone compositions produced from legumes
6	7,030,239	Compounds to treat Alzheimer's disease
7	7,030,162	Treatment of migraine headache
8	7,030,144	Substituted imidazole derivatives: GABAA receptor ligands
9	7,030,109	1,2,3,4,5,6-Hexahydroazepino[4,5-b]indoles containing arylsulfones at the 9-position
10	7,029,717	Sucralose-containing composition and edible products containing the composition
11	7,029,657	Nasal spray steroid formulation and method
12	RE39,072	2-aminopropane-1,3-diol compounds, medicinal use thereof, and intermediates in synthesizing the same
13	7,026,447	53 human secreted proteins
14	7,026,322	Phenylahistin and the phenylahistin analogs, a new class of anti-tumor compounds
15	7,026,126	Method for detecting megsin protein and use thereof
16	7,025,971	Treatment or prophylaxis of diseases caused by pilus-forming bacteria
17	7,025,952	Methods of preparation and use of bodywashes containing additives
18	RE39,056	4-Azasteroids for treatment of hyperandrogenic conditions
19	7,022,733	Substituted 2-phenyl benzofurans as estrogenic agents

20 7,022,727 T Crystalline drug form
21 7,022,707 T Piperazine derivatives
22 7,022,520 T Cell culture media for mammalian cells
23 7,022,335 T Suppository of retaining in lower region of rectum
24 RE39,049 T Methods for inhibiting bone loss
25 7,018,991 T 17.beta.-amino and hydroxylamino-11 .beta.-arylsteroids and their derivatives having agonist or antagonist hormonal properties
26 7,018,652 T Composition and method for treating nonalcoholic steatohepatitis
27 7,018,609 T Compositions containing inclusion complexes
28 7,015,226 T Gonadotropin-releasing hormone receptor antagonists and methods relating thereto
29 7,014,858 T Use methods of treating acne and telangiectasia
30 7,012,134 T Dendritic enriched secreted lymphocyte activation molecule
31 7,012,065 T Cyclosporins for the treatment of immune disorders
32 7,012,064 T Cyclosporins for the treatment of immune disorders
33 7,011,818 T Carrier particles for use in dry powder inhalers
34 7,009,063 T Process for the production of oxandrolone
35 7,008,957 T Bicyclic cyanoheterocycles, process for their preparation and their use as medicaments
36 7,008,954 T Th2 differentiation inhibitors
37 7,008,900 T Double metal cyanide catalysts for producing polyether polyols
38 7,008,647 T Treatment of acne
39 7,008,628 T End modified thermal responsive hydrogels
40 7,005,428 T Medical uses of a selective estrogen receptor modulator in combination with sex steroid precursors
41 7,002,028 T 5-androsten-3.beta.-ol steroid intermediates and processes for their preparation
42 7,001,917 T Pyrazole compounds as anti-inflammatory and analgesic agents
43 7,001,592 T Sunscreen compositions and methods of use
44 6,998,115 T Biodegradable poly(.beta.-amino esters) and uses thereof
45 6,998,113 T Bodywashes containing additives
46 6,997,941 T Method and apparatus for treating annular fissures in intervertebral discs
47 RE38,968 T Methods for inhibiting bone loss using 6-hydroxy-2-(4-hydroxyphenyl)-benzo- [b] thien-3-yl-4-[2-(piperidin-1-yl) ethoxyphenylimethanone hydrochloride
48 6,995,284 T Synthesis of selective androgen receptor modulators
49 6,995,202 T Methods of nucleating thermoplastics using concentrates of saturated bicyclic dicarboxylate salts
50 6,995,188 T S-dimethylarsino-thiosuccinic acid s-dimethylarsino-2-thiobenzoic acid s-(dimethylarsino) glutathione as treatments for cancer

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Results of Search in US Patent Collection db for:
((steroid AND norgestimate) AND ((amorphous OR crystalline) OR non-crystalline)): 36 patents.
*Hits 1 through **36** out of **36***

Jump To

Refine Search steroid and norgestimate and (amorphous or crystalli

	PAT. NO.		Title
1	7,026,447	T	53 human secreted proteins
2	6,951,924	T	Antibodies against secreted protein HTEBYII
✓3	6,855,703	T	Pharmaceutical compositions of conjugated estrogens and methods of analyzing mixtures containing estrogenic compounds
4	6,770,466	T	Human protein tyrosine phosphatase polynucleotides, polypeptides, and antibodies
5	6,759,408	T	Combination regimens using progesterone receptor modulators
6	6,753,164	T	Nucleic acids encoding human serpin polypeptide HMCIS41
7	6,693,103	T	1,2,3,4-tetrahydro-2-thioxo-quinolinyl and 1,2,3,4-tetrahydro-2-oxo-quinolinyl derivatives as progesterone receptor modulators
8	6,610,674	T	Method of treating inflammatory conditions with progesterone analogs
9	6,602,902	T	Dha-pharmaceutical agent conjugates to improve tissue selectivity
10	6,576,636	T	Method of treating a liver disorder with fatty acid-antiviral agent conjugates
11	6,503,894	T	Pharmaceutical composition and method for treating hypogonadism
12	6,498,154	T	Cyclic regimens using quinazolinone and benzoxazine derivatives
13	6,465,005	T	Inhibition of crystallization in transdermal devices
14	6,465,004	T	Solubility enhancement of drugs in transdermal drug delivery systems and methods of use
15	6,444,668	T	Combination regimens using progesterone receptor modulators
16	6,399,593	T	Cyclic regimens using cyclic urea and cyclic amide derivatives
17	6,380,178	T	Cyclic regimens using cyclocarbamate and cyclic amide derivatives
18	6,358,948	T	Quinazolinone and benzoxazine derivatives as progesterone receptor modulators
19	6,284,263	T	Buccal drug administration in the treatment of female sexual dysfunction
20	6,284,262	T	Compact dosage unit for buccal administration of a pharmacologically active agent

21 6,274,159 T Surface modified silicone drug depot
22 6,241,529 T Method for facilitating transmucosal delivery of steroidal active agents
23 6,221,383 T Solubility parameter based drug delivery system and method for altering drug saturation concentration
24 6,221,379 T Buccal drug administration in female hormone replacement therapy
25 6,200,593 T Contraceptive method employing buccal delivery of steroidal active agents
26 6,180,682 T Buccal drug delivery system for use in male contraception
27 6,117,446 T Drug dosage unit for buccal administration of steroidal active agents
28 6,024,976 T Solubility parameter based drug delivery system and method for altering drug saturation concentration
29 5,795,909 T DHA-pharmaceutical agent conjugates of taxanes
30 5,759,577 T Controlled release of steroids from sugar coatings
31 5,656,622 T 15,15-dialkyl-substituted derivatives of estradiol
32 5,656,286 T Solubility parameter based drug delivery system and method for altering drug saturation concentration
33 5,587,496 T 15,15-dialkyl-substituted derivatives of estradiol
34 5,554,381 T Low flux matrix system for delivering potent drugs transdermally
35 5,340,586 T Methods and formulations for use in treating oophorectomized women
36 5,340,585 T Method and formulations for use in treating benign gynecological disorders

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NEWS	4	JAN 13	IPC 8 searching in IFIPAT, IFIUDB, and IFICDB
NEWS	5	JAN 13	New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to INPADOC
NEWS	6	JAN 17	Pre-1988 INPI data added to MARPAT
NEWS	7	JAN 17	IPC 8 in the WPI family of databases including WPIFV
NEWS	8	JAN 30	Saved answer limit increased
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NEWS	11	FEB 22	Updates in EPFULL; IPC 8 enhancements added
NEWS	12	FEB 27	New STN AnaVist pricing effective March 1, 2006
NEWS	13	FEB 28	MEDLINE/LMEDLINE reload improves functionality
NEWS	14	FEB 28	TOXCENTER reloaded with enhancements
NEWS	15	FEB 28	REGISTRY/ZREGISTRY enhanced with more experimental spectral property data
NEWS	16	MAR 01	INSPEC reloaded and enhanced
NEWS	17	MAR 03	Updates in PATDPA; addition of IPC 8 data without attributes
NEWS	18	MAR 08	X.25 communication option no longer available after June 2006
NEWS	19	MAR 22	EMBASE is now updated on a daily basis
NEWS	20	APR 03	New IPC 8 fields and IPC thesaurus added to PATDPAFULL
NEWS	21	APR 03	Bibliographic data updates resume; new IPC 8 fields and IPC thesaurus added in PCTFULL
NEWS	22	APR 04	STN AnaVist $500 visualization usage credit offered
NEWS	23	APR 12	LINSPEC, learning database for INSPEC, reloaded and enhanced
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=> s estrone
L1        15570 ESTRONE

=> s piperate salt
             34 PIPERATE
         763162 SALT
L2            0 PIPERATE SALT
                (PIPERATE(W)SALT)

=> s piperate adj salt
             34 PIPERATE
            238 ADJ
         763162 SALT
L3            0 PIPERATE ADJ SALT
                (PIPERATE(W)ADJ(W)SALT)

=> s estrogen
L4        76430 ESTROGEN

=> s steroids
L5       111337 STEROIDS

=> s l1 and amorphous
         252820 AMORPHOUS
L6           44 L1 AND AMORPHOUS

=> s l1 and non crystalline
         787347 NON
          69770 CRYSTALLINE
            563 NON CRYSTALLINE
                  (NON(W)CRYSTALLINE)
L7            0 L1 AND NON CRYSTALLINE

=> s l4 and amorphous
         252820 AMORPHOUS
L8           17 L4 AND AMORPHOUS

=> s l5 and amorphous
         252820 AMORPHOUS
L9          488 L5 AND AMORPHOUS

=> s l5 and hormone HRT
         275806 HORMONE
           4152 HRT
              1 HORMONE HRT
                  (HORMONE(W)HRT)
L10           0 L5 AND HORMONE HRT

=> d l8 1-17 ibib hitstr abs

L8   ANSWER 1 OF 17  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2003:177237  CAPLUS
DOCUMENT NUMBER:          138:396363
TITLE:                    Deviant peri-oestrual hormone patterns affect the
                          epithelium of the uterine tube in repeat-breeder
                          heifers
AUTHOR(S):                Bage, Renee; Masironi, Britt; Sahlin, Lena;
                          Rodriguez-Martinez, Heriberto
CORPORATE SOURCE:         Department of Obstetrics and Gynecology, Faculty of
                          Veterinary Medicine, Swedish University of
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Agricultural Sciences (SLU), Uppsala, SE-750 07, Swed.
SOURCE: Reproduction, Fertility and Development (2002), 14(7,8), 461-469
CODEN: RFDEEH; ISSN: 1031-3613
PUBLISHER: CSIRO Publishing
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In the bovine reproductive tract, the uterine tube is the critical site for a series of events required for fertilization and early embryonic development. In previous studies, a defined category of subfertile heifers, repeat-breeder heifers (RBH), has presented peri-estrual disturbances (deviating hormone patterns and follicular dynamics) and uterine maternal-embryonic asynchrony. The present study aimed to investigate if tubal function was also affected, by determination of differences in the morphol. of the tubal lining epithelium of RBH (n = 4) in comparison to controls (n = 6) during standing estrus, studied by light and electron microscopy (SEM/TEM), and relate this to steroid hormone concns. and receptor distribution in the target tissues. Tissue distribution of **estrogen** receptor α (ERα) and progesterone receptor B (PRB) was quantified using immunohistochem. In particular, secretory cells differed in appearance between RBH and controls. The cells were less lumen protruding, microvilli were fewer and smaller and secretory granules in the apical cytoplasm were more numerous in RBH. Furthermore, the tubal epithelium was conspicuously coated with **amorphous** material. Morphol. differences between categories were not explained hormonally or by steroid receptor distribution, except in two heifers from which uterine tubes were obtained after the LH surge. The isthmic PRB: ERα ratio was twice as high in the RBH than in the control. The deviating ultrastructure found in RBH, before and after the LH surge, might influence the tubal microenvironment with effects on gamete transport and final maturation and early embryonic development. The present study confirms that previously recorded perturbations in reproductive physiol. in RBH are also manifested in the uterine tube, mainly by a deviating ultrastructure of the lining epithelium.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:746975 CAPLUS
DOCUMENT NUMBER: 135:288952
TITLE: Preparation of 17β-Fluor-7α-{5-[methyl(7,7,8,8,9,9,10,10,10-nonafluordecyl)amino]pentyl}estra-1,3,5(10)-trien-3,17β-diol as a crystalline ansolvate
INVENTOR(S): Winter, Gabriele; Kroll, Jorg; Vettel, Stephan; Beckmann, Wolfgang
PATENT ASSIGNEE(S): Schering AG, Germany
SOURCE: Ger. Offen., 8 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10011883	A1	20011011	DE 2000-10011883	20000307

PRIORITY APPLN. INFO.: DE 2000-10011883 20000307
GI

10022138

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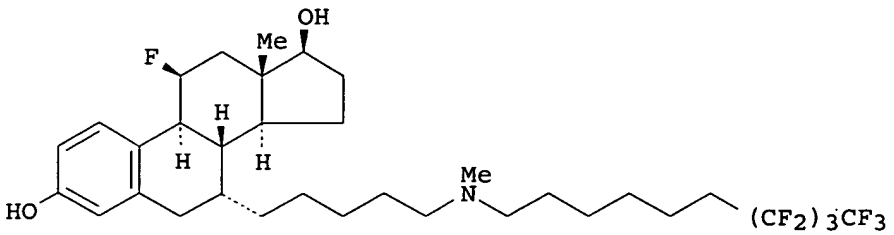

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AB The present invention describes crystalline 11β-Fluor-7α-{5-[methyl(7,7,8,8,9,9,10,10,10-nonafluordecyl)amino]pentyl}estra-1,3,5(10)-trien-3,17β-diol (I) in form of the ansolvate with a m.p. of 141° (DTA) and is characterized by removal, in particular from ethanol, or by displacement crystallization from a solvent, such as ethanol, with water; to aid the crystallization seed crystals from a preceding crystallization can be added.; with the crystallization a pure compound is obtained. Thus, **amorphous** I was dissolved in EtOH; H2O was added and solution heated to 40°; a crystalline seed of I is added; the crystalline material is collected. The crystalline form I can be converted analogously like the **amorphous** form to pharmaceutical prepns., which can be used for the therapy of **estrogen** dependent diseases, e.g. mammary carcinoma, endometrial carcinoma, prostate hyperplasia, anovular infertility and melanoma.

L8 ANSWER 3 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:392221 CAPLUS
DOCUMENT NUMBER: 133:103142
TITLE: Myocardial ischemia-reperfusion injury in **estrogen** receptor-α knockout and wild-type mice
AUTHOR(S): Zhai, Peiyong; Eurell, Thomas E.; Cooke, Paul S.; Lubahn, Dennis B.; Gross, David R.
CORPORATE SOURCE: Department of Veterinary Biosciences, University of Illinois, Urbana-Champaign, IL, 61802, USA
SOURCE: American Journal of Physiology (2000), 278(5, Pt. 2), H1640-H1647
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors investigated the function of **estrogen** receptor-α in global myocardial ischemia and reperfusion injury in male **estrogen** receptor-α knockout (ERKO) and wild-type mice. Mouse hearts were subjected to 45 min of global ischemia followed by 180 min of reperfusion. The hearts were excised, cannulated, and maintained in a chilled (4°) cardioplegia solution until warm (37°) oxygenated Krebs-Henseleit bicarbonate buffer was perfused through the coronary arteries. ERKO hearts started beating later and had a higher incidence of ventricular fibrillation and/or tachycardia than control hearts. Coronary flow rate was significantly lower in ERKO hearts

during the 90- and 120-min periods of reperfusion. Ca2+ accumulation was significantly greater following 30, 90, 120, 150, and 180 min of reperfusion in ERKO hearts. Nitrite production was significantly less in ERKO hearts following 90, 120, and 150 min of reperfusion. Myocardial reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide was significantly lower in exptl. ERKO hearts. Marked interstitial edema and contraction bands were seen in hematoxylin-eosin-stained sections of ischemia-reperfused ERKO hearts but not in control tissues. Hematoxylin-basic fuchsin-picric acid-stained sections from exptl. ERKO hearts had fewer viable myocytes compared with controls. TEM revealed swollen and fragmented mitochondria with **amorphous** and granular bodies, loss of matrix, and rupture of cristae in exptl. ERKO hearts. This is the first demonstration that **estrogen** receptor-α plays a cardioprotective role in ischemia-reperfusion injury in males.

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:175825 CAPLUS
DOCUMENT NUMBER: 132:208004
TITLE: Preparation of 11β-fluoro-7α-(14,14,15,15,15-pentafluoro-6-methyl-10-thia-6-azapentadecyl)estra-1,3,5(10)-triene-3,17β-diol as a crystalline solvate
INVENTOR(S): Beckmann, Wolfgang; Winter, Gabriele; Ewers, Christian; Westermann, Jurgen
PATENT ASSIGNEE(S): Schering A.-G., Germany
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000014104	A1	20000316	WO 1999-DE2894	19990906
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 19842123	C1	20000713	DE 1998-19842123	19980905
PRIORITY APPLN. INFO.:			DE 1998-19842123 A	19980905

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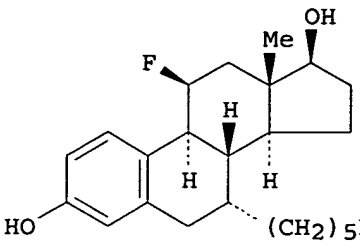

I

AB The present invention relates to crystalline 11β-fluoro-7α-(14,14,15,15,15-pentafluoro-6-methyl-10-thia-6-azapentadecyl)estra-1,3,5(10)-triene-3,17β-diol (I) in the form of a solvate. The crystalline solvate of I is produced by extracting I from water or water/ethanol by means of stirring or by extracting said I from a solvent such as ethanol or methanol with water by means of displacement crystallization Seed crystals can be added to the compound from a prior crystallization stock in order to achieve said crystallization Crystallization is associated with purification of I. The crystalline form of I can be processed in a similar manner to the **amorphous** form thereof for pharmaceutical prepns. that can be used to treat **estrogen** -related illnesses such as mammary carcinoma.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:339021 CAPLUS
DOCUMENT NUMBER: 131:139652
TITLE: **Estrogen** induces cytokeratin aggregation in primary cultures of Armenian hamster hepatocytes
AUTHOR(S): Satoh, Mutsumi I.; Hayes, Stanley F.; Coe, John E.
CORPORATE SOURCE: Public Health Service, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Rocky Mountain Laboratories, U.S. Department of Health and Human Services, Hamilton, MT, USA
SOURCE: Cell Motility and the Cytoskeleton (1999), 43(1), 35-42
CODEN: CMCYEO; ISSN: 0886-1544
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of **estrogen** administration to cultured Armenian hamster was studied. Isolated Armenian hamster hepatocytes were cultured in RPMI medium supplemented with β-estradiol (E2). β-Estradiol treatment for 24-48 h induced cytoplasmic inclusion bodies which by immunocytochem. were pos. for cytokeratin (CK) 8, CK 18, and ubiquitin but neg. for CK 7 and CK 19. These inclusion bodies appeared as filamentous tangles or **amorphous** aggregates when observed by electron microscopy. F-actin, tubulin, and desmosomes were not influenced by the presence of the inclusion bodies. Addition of ethanol to culture medium increased the incidence of the inclusion formation. In combination with 0.5% ethanol 1 μM of E2 induced five to six times more inclusion bodies, while the number of inclusion bodies decreased when epidermal growth factor (EGF) was added to the medium in combination with E2. This reduction effect was nullified by treatment with anti-EGF receptor antibody. These

findings suggest that E2 treatment to Armenian hamster hepatocytes in vitro induces Mallory body-like inclusions whose incidence can be influenced by addition of ethanol or EGF to the culture medium.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:161136 CAPLUS
DOCUMENT NUMBER: 128:221639
TITLE: Preparation of **amorphous** benzothiophenes for pharmaceuticals
INVENTOR(S): Cuff, George W.; Thakkar, Arvind L.
PATENT ASSIGNEE(S): Eli Lilly and Company, USA; Cuff, George W.; Thakkar, Arvind L.
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9808513	A1	19980305	WO 1997-US14768		19970822
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
EP 826682	A1	19980304	EP 1997-306426		19970822
EP 826682	B1	20030312			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
CA 2263175	AA	19980305	CA 1997-2263175		19970822
AU 9742335	A1	19980319	AU 1997-42335		19970822
AU 723987	B2	20000907			
IN 182940	A	19990814	IN 1997-CA1549		19970822
BR 9713176	A	20000208	BR 1997-13176		19970822
CN 1244124	A	20000209	CN 1997-197434		19970822
NZ 333839	A	20010629	NZ 1997-333839		19970822
IL 128641	A1	20011031	IL 1997-128641		19970822
TR 9900403	T2	20020121	TR 1999-9900403		19970822
JP 2002514174	T2	20020514	JP 1998-511744		19970822
AT 234295	E	20030315	AT 1997-306426		19970822
ES 2195089	T3	20031201	ES 1997-306426		19970822
ZA 9707617	A	19990225	ZA 1997-7617		19970825
US 6713494	B1	20040330	US 1997-918741		19970825
NO 9900914	A	19990225	NO 1999-914		19990225
KR 2000035941	A	20000626	KR 1999-701682		19990227
PRIORITY APPLN. INFO.:			US 1996-24831P	P	19960828
			WO 1997-US14768	W	19970822

OTHER SOURCE(S): MARPAT 128:221639

AB A method for preparing an **amorphous** form of a benzothiophene such as raloxifene is described. Thus, raloxifene-HCl was prepared by a series of reactions starting from 3-methoxybenzenethiol and 4'-methoxyphenacyl bromide. A formulation contained PEG-1450 70, spray-dried lactose 1.5, colloidal SiO2 1.5, Polysorbate-80 2.0, and raloxifene-HCl 25%. The bioavailability of raloxifene-HCl and the pharmacol. effects of this

compound on osteoporosis and hyperlipidemia were determined
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 7 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:2539 CAPLUS
DOCUMENT NUMBER: 124:45982
TITLE: Immunohistochemical study of **estrogen**-induced lactoferrin-like protein in the mouse uterus: Localization in the nucleolus and secretory pathway
AUTHOR(S): Yamashita, Shuji
CORPORATE SOURCE: Keio Junior College Nursing, Shinjuku, 160, Japan
SOURCE: Acta Histochemica et Cytochemica (1995), 28(3), 217-25
CODEN: ACHCBO; ISSN: 0044-5991
PUBLISHER: Japan Society of Histochemistry and Cytochemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Lactoferrin (LF) is known as an **estrogen**-inducible protein in the murine uterus. This study, employing immunoelectron microscopy with the pre-embedding methods, was carried out to elucidate temporal LF induction, the process of the induction and intracellular localization after 17 β-estradiol (E2) stimulation in the endometrial epithelium of ovariectomized adult mice. By single i.p. injection of E2 (20 μg/kg), LF was rapidly induced, even after 1 h, and was exclusively localized in the nucleoli of surface and glandular epithelium. At 7 h after E2 injection, strong immunostaining was recognized in the **amorphous** cytoplasm and in nucleoli, especially in the dense fibrillar component of the epithelium. From 13 h to 23 h after E2 administration, strong reaction was observed in the secretory pathway, i.e., cisternae of endoplasmic reticulum and the Golgi apparatus, and in vesicles and vacuoles in the apical cytoplasm, in addition to the nucleolar staining. LF-immunoreaction was also detected in the nucleoli and cytoplasm of stromal and muscle cells; it was demonstrated in the epithelium at the earliest period, subsequently in the stromal cells (7 h), and finally in the muscle cells (13 h). After three days of consecutive E2 stimulation, many secretory granules in the apical cytoplasm and apical cell membrane showed intense LF immunoreaction. The present study suggests that LF in the nucleolus plays an important role in activation of ribosomal biogenesis preceding the cell differentiation and proliferation in the mouse uterus.

L8 ANSWER 8 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1990:48967 CAPLUS
DOCUMENT NUMBER: 112:48967
TITLE: Endometrial response to deciduogenic stimulus in ovariectomized rhesus monkeys treated with **estrogen** and progesterone: an ultrastructural study
AUTHOR(S): Sengupta, J.; Given, R. L.; Talwar, D.; Ghosh, D.
CORPORATE SOURCE: Dep. Physiol., All India Inst. Med. Sci., New Delhi, 110029, India
SOURCE: Journal of Endocrinology (1990), 124(1), 53-7, 2 plates
CODEN: JOENAK; ISSN: 0022-0795
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The present work continues the aim of establishing an exptl. model to study the decidual cell reaction to an artificial deciduogenic stimulus in the long-term ovariectomized rhesus monkey treated with **estrogen** followed by progesterone. The fine structural details of decidual,

granular, and plaque cells, which constituted the endometrial cellular response to the deciduogenic stimulation in the present study, revealed striking similarities with those reportedly present in a endometrial response to blastocyst implantation in the rhesus monkey. Plaque epithelia showed a significant degree of hypertrophy, hyperplasia and differentiation followed by a steady degeneration by day 32 (equivalent to day 16 after trauma) of treatment. The plaque cells contained numerous regular-shaped mitochondria, polyribosomes, and large amts. of rough endoplasmic reticulum (RER) in their cytoplasm and were characteristically arranged in clusters or acini formation surrounded by discrete basal laminae. As early as day 28 of treatment, the initiation of stromal decidual cell transformation was noted and, by day 48, a sizeable pool of decidual cells was found. The decidual cells had rounded nuclei and elaborate arrangements of interconnected cisternae of RER which were often moderately dilated and filled with **amorphous**, electron-dense material. Granular cells were characterized by eccentrically located nuclei and numerous membrane-bound, electron-dense granules in their cytoplasm and were found in increasing nos. in the stroma around decidual cells, blood vessels, and glandular epithelia. Based on the ultrastructural and temporal characteristics of the endometrial cells studied it has been suggested that the cells have secretory functions, and that the differential maturation profiles of the cell types might be caused by their differences in sensitivities and by their integral response to progesterone.

L8 ANSWER 9 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1988:420513 CAPLUS
DOCUMENT NUMBER: 109:20513
TITLE: Ultrastructural demonstration of avidin/biotin-binding protein by block-staining methods in oviduct responses of hens and estradiol-primed chicks
AUTHOR(S): Kami, Koji; Yasuda, Kenjiro
CORPORATE SOURCE: Sch. Med., Keio Univ., Tokyo, 160, Japan
SOURCE: Okajimas Folia Anatomica Japonica (1988), 64(6), 319-33
CODEN: OFAJAE; ISSN: 0030-154X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Previous studies have demonstrated that progesterone stimulates rapid and simultaneous biosynthesis of egg-white proteins in the tubular gland cells and in some epithelial cells of the oviduct in **estrogen**-primed chicks. The present investigation was undertaken to compare hens with **estrogen**-primed chicks, and to identify the precise site of progesterone-induced avidin biosynthesis in the oviduct. Endogenous biotin-binding sites were revealed in secretory granules of tubular gland cells and in epithelial cells. Biotin-binding sites were also observed in the **amorphous** matrix of the rough endoplasmic reticulum cisternae in the acinar cells of hormone-treated chicks. Immunoreactive avidin was similarly found in secretory granules of tubular gland cells by block-staining methods with anti-avidin (Fab')2 antibody. In the present study, the cytochem. localization of the biotin-binding sites in immunogenic avidin was identical with that of progesterone-receptor sites.

L8 ANSWER 10 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1986:620537 CAPLUS
DOCUMENT NUMBER: 105:220537
TITLE: Histopathological study of Oryzias latipes (Medaka) after long-term β-hexachlorocyclohexane exposure
AUTHOR(S): Wester, P. W.; Canton, J. H.
CORPORATE SOURCE: Lab. Pathol., Natl. Inst. Public Health Environ. Hyg.,

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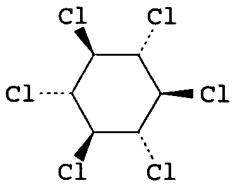
Bilthoven, Neth.
SOURCE: Aquatic Toxicology (1986), 9(1), 21-45
CODEN: AQTODG; ISSN: 0166-445X
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Two toxicity expts. were carried out with β-HCH (I) [319-85-7] in the Japanese ricefish (medaka, O. latipes). The expts. were started with freshly fertilized eggs (Exp. I) or with young fish (1 mo post hatching) (Exp. II). The concentration of β-HCH ranged from 0.032-1.0 mg/L tank water. After 1 and 3 mo histopathol. examination was carried out, which revealed development of testis-ova (intersexuality, hermaphroditism) in males and induction of vitellogenesis in either sex after 3 mo. These features are characteristic of **estrogen**-like activity. In addition, after 1 and 3 mo heterotopic development of adipose tissue (lipomatosis) was observed in parenchymal organs (liver, kidney, testis) which in the liver was associated with multilocular dilations of the interstitium (spongiotic edema) in Exp. I. In this experiment, the vacuolation of liver cells was also increased, which electronmicroscopically appeared to be due to accumulation of glycogen [9005-79-2]. In the thyroid follicles the epithelial cells showed hypertrophy and the colloid content was diminished; moreover, the number of thyrotropic hormone-producing cells in the pituitary was increased. These observations are indicative of a high level of activity of the thyroid. In the kidneys accumulation of **amorphous** eosinophilic precipitate in the glomeruli (glomerular hyalinosis) was prominent, and a similar precipitate could be found around the liver sinusoids and the splenic capsule; the nature of this precipitate could not be determined histochem. and electronmicroscopically. Apparently, β-HCH has multiple toxic effects in medakas, some of which yield evidence for an **estrogen**-like activity, as is also found in guppies and rodents. Exposure to 1 or 3 mo in both expts. produced no-effect concns. of 0.056 and 0.1 mg β-HCH/L resp.

L8 ANSWER 11 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1971:61974 CAPLUS
DOCUMENT NUMBER: 74:61974
TITLE: Calcium carbonate in medullary bone
AUTHOR(S): Pellegrino, Edmund D.; Biltz, Robert M.
CORPORATE SOURCE: Dep. Med., State Univ. New York, Stony Brook, NY, USA
SOURCE: Calcified Tissue Research (1970), 6(2), 168-71
CODEN: CATRBZ; ISSN: 0008-0594
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The physiol. importance of bone $CaCO_3$ of laying hens is not restricted to its role as an eggshell Ca reserve, nor can it be assigned only to intramedullary bone. It is not always possible to demonstrate $CaCO_3$ in untreated bone by crystallog. methods, even when relatively large amts.

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are indicated by chemical anal., but under certain conditions it may be seen to crystallize. Ir anal. can be employed to distinguish between CO3-apatite and crystalline CaCO3 in bone. Medullary bone may differ in composition from the compact cortical bone adjacent to it. In the ir spectra of the **estrogen**-induced medullary bone of the male pigeon, significantly more organic material (chondroitin sulfate) was present than in adjacent cortical bone; there was also proportionately more **amorphous** Ca phosphate and less CO3-apatite. Intermediate differences in bone composition were observed in another specimen of medullary bone obtained from a laying hen. Both cortical and medullary bone from a different laying hen contained crystalline CaCO3. The authors conclude that crystalline CaCO3 is present in vivo.

L8 ANSWER 12 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1965:416984 CAPLUS
DOCUMENT NUMBER: 63:16984
ORIGINAL REFERENCE NO.: 63:3005g-h,3006a-c
TITLE: Cyclosenegenin, a derivative of senegenin in Polygala senega
AUTHOR(S): Shimizu, Y.; Pelletier, S. W.
CORPORATE SOURCE: Univ. of Georgia, Athens
SOURCE: Journal of the American Chemical Society (1965), 87(9), 2065-6
CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE: Journal
LANGUAGE: English
GI For diagram(s), see printed CA Issue.
AB Cyclosenegenin (I) is proposed to be the primary sapogenin obtained from the hydrolysis of senegenin (II) (Jacobs and Isler, CA 31, 62454). II was treated with aqueous H2SO4 and then acetylated to give two crystalline acids (as acetates): senegenic acid (III) and IV. IV was hydrolyzed by alkali to V, which could be reacetylated to IV. The **amorphous** Me ester of IV gave an N.M.R. spectrum which showed V to contain two CO2H and three OH groups. V was refluxed with dilute H2SO4 to give a diene (VI) identical to that obtained from II by treatment with quinoline. I is thus the "hydroxy-senegenin" proposed by Dugan, et al. (CA 60, 10728d), which gives III by a reverse Prins reaction. Treatment of II with 2N NaOH gave I, which reverted quant. to II on brief warming with dilute HCl. Treatment of II with dilute H2SO4 gave V and a little VI. The structure proposed for I was supported by uv, ir, and N.M.R. data.

L8 ANSWER 13 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1965:410314 CAPLUS
DOCUMENT NUMBER: 63:10314
ORIGINAL REFERENCE NO.: 63:1831h,1832a-g
TITLE: 17α-Chloroethynyl steroid ketones
INVENTOR(S): Smith, Herchel
SOURCE: 21 pp.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
NL 6409391	A	19650215	NL 1964-9391	19640814
IL 21826	A1	19681226	IL 1964-21826	19640803

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NO 126016	B	19721211	NO 1964-154276	19640805
IN 95058	A	19750816	IN 1964-95058	19640805
BR 6461643	A0	19730809	BR 1964-161643	19640810
CH 498819	A	19701115	CH 1964-498819	19640812
CH 498820	A	19701115	CH 1964-498820	19640812
CH 498821	A	19701115	CH 1964-498821	19640812
CH 499510	A	19701130	CH 1964-499510	19640812
CH 507225	A	19710515	CH 1964-507225	19640812
FR 1566154	A	19690509	FR 1964-1566154	19640813
AT 301039	B	19720825	AT 1968-2927	19640813
AT 301045	B	19720825	AT 1970-2274	19640813
DK 134161	B	19760920	DK 1964-4004	19640813
SE 331470	B	19710104	SE 1964-9834	19640814
SE 334879	B	19710510	SE 1968-4239	19640814
SE 335119	B	19710517	SE 1968-4237	19640814
SE 335120	B	19710517	SE 1968-4238	19640814
SE 350256	B	19721023	SE 1970-8431	19640814
NO 127193	B	19730521	NO 1966-165753	19661125
NO 132762	B	19750922	NO 1966-165752	19661125
DK 127598	B	19731203	DK 1969-6552	19691210
JP 48037029	B4	19731108	JP 1971-57584	19710802
DK 132031	B	19751013	DK 1971-3957	19710812
NO 129905	B	19740610	NO 1971-4959	19711230
DK 127475	B	19731112	DK 1972-2202	19720503
DK 131020	B	19750520	DK 1973-382	19730124
DK 131367	B	19750707	DK 1973-847	19730216
DK 134264	B	19761011	DK 1973-2861	19730524
NL 7308507	A	19730925	NL 1973-8507	19730619
NL 7308508	A	19730925	NL 1973-8508	19730619
IN 137555	A	19750816	IN 1974-137555	19740503
IN 137556	A	19750816	IN 1974-CA1000	19740503
IN 137557	A	19750816	IN 1974-CA1001	19740503

PRIORITY APPLN. INFO.:

GB 1963-32064	A	19630814
IN 1964-95058	A1	19640805
NO 1964-154276	A	19640805
DK 1964-4004	A	19640813

AB (±)-13β-Ethyl-3-methoxygona-2,5(10)-dien-17-one (I) (8 g.) added with stirring to 5.53 g. LiMe and 16.9 g. cis-(:CHCl)2 (II) in 100 cc. Et2O under N and stirred 48 hrs. at room temperature yielded 4.5 g. (±)-17α-chloroethynyl-13β-ethyl-3-methoxygona-2,5(10)-dien-17β-ol (IIa). 13β-Pr analog (8 g.) of I gave similarly 2.5 g. 13β-Pr analog (III) of IIa, m. 110-16° (MeOH). II (11 g.) added during 1 hr. to 94.6 g. LiMe in 300 cc. Et2O, treated with 12 g. (±)-13β-ethyl-D-homo-3-methoxygona-2,5(10)-dien-17a-one in 200 cc. Et2O and stirred at room temperature yielded 13 g. (±)-17aα-chloroethynyl-13β-ethyl-D-homo-3-methoxygona-2,5(10)-dien-17aβ-ol(IV), m. 120-6° (decomposition). IIa (2.5 g.) in 100 cc. MeOH and 200 cc. dioxane stirred 2 hrs. with 2 g. (CO2H)2.2H2O yielded 1.9 g. (±)-17α-chloroethynyl-13βethylgon-5(10)-en-17β-ol-3-one (V), m. 115-20° (Et2O hexane). (CO2H)2.2H2O (1.2 g.) in 10 cc. H2O added with stirring to 1.0 g. III in 150 cc. iso-PrOH under N and stirred 2 hrs. yielded 0.35 g. 13β-Pr analog of V, m. 174-6° (Et2O-hexane). IV (2.5 g.) in 20 cc. tetrahydrofuran and 80 cc. MeOH containing 10 cc. H2O and 1.75 g. (CO2H)2.H2O, diluted with 20 cc. tetrahydrofuran, and stirred 45 min. under N yielded 1.4 g. (±)-17aα-chloroethynyl-13β-ethyl-D-homogon-5(10)-en-17β-ol-3-one, m. 150-4°. Crude IIa (3 g.)in 36cc. MeOH containing 2.4 cc. 11N HCl and 1.6 cc. H2O stirred 0.5 hr. gave 1 g. (±)-17α-chloroethynyl-13β-ethylgon-4-en-17β-ol-3-one (VI), m. 152-4°, resolidifying and remelting at 183-4° (decomposition)

(AcOEt-hexane), m. 187-90° (decomposition) (after chromatography and recrystn. from aqueous 3:1 H2O-MeOH. Crude III (5.5 g.) gave similarly 1.1 g. 13β-Pr analog (VII) of VI, m. 179-81° (AcOEt-hexane). IV (13 g.) yielded similarly 7.4 g. (±)-17aα-chloroethynyl-13β-ethyl-D-homogon-4- en- 17aβ-ol-3-one (VIII), m. 204-6° (AcOEt-hexane). VI (0.5 g.) and 5 cc. 2,3-dihydropyran, 0.8 cc. C6H6, and 0.014 g. p-MeC6H4SO3H.H2O kept 16 hrs. at room temperature gave 0.36 g. 17β-(2-tetrahydropyranyl) ether of VI, m. 125-31° (hexane). VI (3.0 g.), 48 cc. Ac2O, 24 cc. AcCl, and 2.4 cc. C5H5N refluxed 2 hrs. gave (±)-17α-chloroethynyl-3,17β-diacetoxy-13β-ethylgona-3,5-diene (IX), m. 177-80°. IX (2.5 g.) in 70 cc. MeOH and 70 cc. tetrahydrofuran stirred 1 hr. at 0° with 200 cc. 2% KOH-MeOH gave 1.27 g. (±)-17β-acetoxy- 17α- chloroethynyl-13β- ethylgon-4 - en-3-one (X), m. 185-7° (Et2O-hexane). VI (3.0 g.), 70 cc. (C7H15CO)2O, 2.4 cc. C5H5N, and 25 cc. C7H15COCl heated 3.5 hrs. at 100° yielded 3.7 g. 3,17β-diheptanoyloxy analog of IX, m. 56-65° (MeOH). IX (3.5 g.) in 360 cc. MeOH stirred 2 hrs. at 0° under N with 120 cc. 2% KOH-MeOH yielded 3.7 g. 17β-C7H15CO2 analog (XI) of X. (±)-17α-Chloroethynyl-13β-ethylgon-4-en-17β-ol-3-one (5 g.) stirred 3 hrs. with 2 g. NaBH4 in 250 cc. EtOH yielded 5 g. (±)-17α-chloroethynyl-13β-ethylgon-4-en-3,17β-diol (XII), **amorphous** powder, probably a mixture of the 3α- and 3βepimers. (±)-17α - Chloroethynyl - 13β - ethylgon - 4 - en - 3 - one (2.2 g.) in 100 cc. tetrahydrofuran stirred 2 hrs. with cooling with 2.2 g. (tert-BuO)3AlLiH gave 0.8 g. 3β-epimer (XIII) of XII, m. 120-4° (Et2O-petr. ether). X (0.5 g.) in 20 cc. tetrahydrofuran treated overnight with 0.5 g. (tert-BuO)3AlLiH gave 0.45 g. (±)-17β-acetoxy-17α-chloroethynyl- 13β-ethylgon-4- en-3β-ol (XIV). XI (0.59 g.) in 25 cc. MeOH stirred 2 hrs. at room temperature with excess NaBH4 yielded 0.5 g. (±)-17α-chloroethynyl-13β-ethyl-17β-heptanoyloxygon-4-en-3-ol (XV). XII (2 g.) in 10 cc. C5H5N with 15 cc. Ac2O gave 0.9 g. 3-acetate (XVI) of XII, m. 154-60° (aqueous MeOH). XIII (1.4 g.) in 7 cc. C5H5N with 10.5 cc. Ac2O gave 0.8 g. 3-acetate of XIII, m. 163-5°. XIV (0.45 g.) gave similarly 0.2 g. 3-acetate of XIV, m. 144-5° (Et2O). XV (0.5 g.) in 5 cc. C5H5N stirred 20 hrs. with 0.12 g. AcCl in 4 cc. C6H6 yielded 0.2 g. 3-acetate of XV. XIII (0.8 g.) in 25 cc. C5H5N stirred 3 days with 1.0 g. succinic anhydride gave 0.5 g. 3β-hemisuccinate of XIII, m. 155-7°, which with NaHCO3 yielded the Na salt, m. 160-70° (decomposition) (Et2O-EtOH). XlII (1.0 g.), 1 cc. C5H5N, and 1.1 cc. (C7H15CO)2O kept 24 hrs. gave 0.65 g. 3β-heptanoate of XIII, m. 142-4° (MeOH). Examples for the formulation of VI as oral progestational agent are given. The progestational activity was determined for the following compds. in comparison with progesterone (XVII) = 100: V 100, (+)-17α-chloroethynyl-13β-methylgon-4-en-17β-ol-3-one (XVIII) 300, VI 1000, VII 100, VIII 400, X 1500. The pituitary gonadotropin inhibiting activity of the following compds. was determined: XVIII 100, VI 260, VIII 150, V 225, XII 110, XVI 180. The **estrogen**-antagonistic activity of XVIII, VI, and VIII was 6600, 10800, and 200, resp., as compared to XVII = 100.

L8 ANSWER 14 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1956:44487 CAPLUS
DOCUMENT NUMBER: 50:44487
ORIGINAL REFERENCE NO.: 50:8576f-i,8577a-h
TITLE: Synthesis of a potential **estrogen**, 1,3-dimethyl-7-hydroxy-phenanthrene-2-carboxylic acid
AUTHOR(S): van der Meer, S.; Veldstra, H.
CORPORATE SOURCE: Bandoengsche en Nederlandsche Kininefabriek, Amsterdam
SOURCE: Recueil des Travaux Chimiques des Pays-Bas et de la

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Belgique (1955), 74, 1269-80
CODEN: RTCPB4; ISSN: 0370-7539
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 50:44487

AB The crude nitration product from 3-HOC6H4CHO (70.6% yield) was boiled with C6H6 and filtered hot to obtain from the insol. material 27.6% 6,3-O2N(HO)C6H3CHO (I), m. 165-6°, and from the C6H6 exts. 19.4% 4,3-O2N(HO)C6H3CHO, m. 128-9° (from alc.) [the alc. mother liquors on concentration gave 10.1% 2,3-O2N(HO)C6H3CHO, m. 152-3°]. 2,6-Me2C6H3CO2H (IA) (50 g.), 250 g. paraformaldehyde, 500 mL. glacial AcOH and 500 mL. concentrated HCl were heated 5 h. on the steam bath, the whole cooled, diluted with 1 l. H2O and filtered to obtain a filtrate (II) and a solid which gave 44.2 g. 2,6,3-Me2(ClCH2)C6H2CO2H (III), m. 137-8° (from C6H6) [III in glacial AcOH over Pd/BaSO4 and H gave 2,3,6-Me3C6H2CO2H, m. 107.5-8.5° (from petr. ether)]. II subjected to paper chromatog. showed the presence of 2,6,3,5-Me2(ClCH2)2C6HCO2H (IV); as above, IV gave 2,3,5,6-Me4C6HCO2H, m. 174-5°. To 160 g. KCN in 240 mL. H2O, at 0°, was added 40 g. III slowly, with stirring and the mixture stirred 0.5 h. at room temperature, warmed to 98° during 0.75 h., kept 0.5 h. at 98°, cooled, and acidified carefully with 4N HCl gave part of the 2,6,3-Me2(NCCH2)C6H2CO2H (V). The filtrate from V was freed of HCN in vacuo, then extracted with Et2O, the Et2O exts. were combined with the V, and the Et2O solution was dried, concentrated, and distilled to give 36.2 g. V, colorless needles, m. 158-9° (from C2H4Cl2). IV (1 g.), 2 g. Zn(CN)2, and 10 mL. H2O heated 2.5 h. on a steam bath, acidified with HCl, and extracted with Et2O, the Et2O exts. were concentrated, CHCl3 added, and the CHCl3 distilled to remove residual Et2O, and cooled gave 2,6,3-Me2(HOCH2)C6H2CO2H (VI), colorless crystals, m. 158-9°. IV and dilute NaOH also gave VI. Employing BuOH-H2O-70% EtNH2 solution (150:25:1) as a solvent for paper chromatog., followed by spraying with a solution of 1 g. xylose and 1 g. p-EtOC6H4NH2 in 40 mL. alc. and 10 mL. H2O, and warming 20 min. at 80-95° gave satisfactory separation of these acids; the following lists the Rf values using this technique: BzOH, 0.48-0.49; IA, 0.60-0.62; III, 0.69-0.71; IV, 0.75-0.76; V, 0.50-0.51; and VI, 0.37-0.38. V (42.7 g.), 42.7, g. NaOH, and 171 mL. H2O were refluxed 1.25-1.5 h., cooled and the solution acidified with dilute H2SO4 to give 43.3 g. 2,6,3-Me2(HO2CCH2)C6H2CO2H (VII), colorless needles, m. 201-2° (from H2O). VII (20.8 g.), 16.8 g. NaHCO3, and 20 mL. H2O were mixed, evaporated to dryness and the di-Na salt (VIII) dried at 100°. Ac2O (102 g.), 16.7 g. I, and VIII were heated 46 h. (temperature not specified), cooled, diluted with 102 mL. H2O, heated carefully to boiling, boiled 1 min., cooled, diluted with 400 mL. H2O and extracted with Et2O, the dried Et2O exts. were concentrated, the orange sirup dissolved in 600 mL. 4% NaOH at 50°, the mixture heated to 82° in 10 min., cooled, acidified with dilute H2SO4, and extracted with Et2O, and the Et2O exts. concentrated gave 35.5 g. brown **amorphous** solid (IX), which, recrystd. twice from 1:5 AcOH-H2O and twice from H2O, gave 2,6,3-Me2[HO2CC(:CHC6H3(OH)NO2-3,6)]C6H2CO2H.H2O (X), tan crystals, m. about 148-55°. To 272 g. FeSO4.7H2O in 272 mL. cold H2O was added 16.2 g. X in 14 mL. concentrated aqueous NH3 and 45 mL. H2O during 5-10 min., the whole heated to and maintained 0.25 h. at 97°, cooled, and filtered, and the filtrate acidified with 90 mL. 4N HCl to give (XI) which could be filtered only with difficulty; XI was dissolved in boiling alc., the solution evaporated to dryness, and the residue washed with H2O and recrystd. successively from EtOH and

MeOH to give 11.3 g. amino derivative-H2O (XII), gray-white microcrystals, m. 255°. To 112 mL. warm 10% H2SO4 was added 9.6 g. XII, and the solution stirred and diluted with 336 mL. H2O to give a suspension of the sulfate (XIII); to XIII was added at 0°, 2.76 g. NaNO2 in 40 mL. H2O in 0.5 h., the mixture stirred an addnl. 0.5 h., 4.2 g. (H2N)2CO added, the whole stirred 1 h., 75 mL. 4N NaOH added, the ice bath removed and 7.5 g. Cu powder added, the mixture stirred 1 h. at room temperature, 0.5 h. at 50°, 15 min. on the steam bath, cooled and acidified with 75 mL. 4N H2SO4 gave 5.6 g. 1,3-dimethyl-7-hydroxyphenanthrene-2,10-dicarboxylic acid (XIV), m. 275-6° (from H2O). XIV (4.625 g.), 0.462 g. Cu powder and 92.5 mL. dry quinoline, under N, heated 1 h. at 252-65°, the mixture cooled, stirred with Et2O, the Et2O solution extracted with 0.6N NaOH, the NaOH exts. washed with Et2O, then acidified, the solid filtered off and dissolved in 3 mL. 22% aqueous NH3 and 400 mL. H2O, the solution treated with C, filtered and the filtrate acidified with dilute AcOH gave 55% 1,3-dimethyl-1-hydroxyphenanthrene-2-carboxylic acid-H2O (XV), feather-like crystals, m. 279-81°. By analyses and mixed m.p. detns., XV was shown to be different from XIV; a mixed m.p. determination showed XV was different from the isomeric 10-carboxylic acid (XVI, see below). XIV (0.1 g.), 0.01 g. Cu chromite catalyst and 1 mL. dry quinoline were refluxed 1 h. under N, cooled, extracted with Et2O, the Et2O solution washed with dilute NaOH, and the Et2O solution evaporated to give 1,3-dimethyl-7-hydroxyphenanthrene (XVII), m. 170-1° (from petr. ether followed by sublimation). XVI treated similarly also gave XVII. I and 2,4-Me2C6H3CH2CO2K as above gave 36% 2,4-Me2C6H3C[:CH-C6H3(OH)NO2-3,6]CO2H, yellow platelets, m. 199-200° (from 25% AcOH) and the corresponding amino derivative-0.5 H2O (XVIII), colorless crystals, m. about 200-10°. XVIII gave XVI, colorless needles, m. 225-6° (from aqueous alc.). XV had only slight estrogenic activity by the Allen-Doisy test.

L8 ANSWER 15 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1955:79060 CAPLUS
DOCUMENT NUMBER: 49:79060
ORIGINAL REFERENCE NO.: 49:14973c-e
TITLE: Guinea pig copulatory reflex in response to adrenal steroids and similar compounds
AUTHOR(S): Byrnes, Wm. W.; Shipley, Elva G.
CORPORATE SOURCE: Upjohn Co., Kalamazoo, MI
SOURCE: Endocrinology (1955), 57, 5-9
CODEN: ENDOAO; ISSN: 0013-7227
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB Adrenal steroids and related compds. were tested for the ability to evoke the copulatory reflex which can be induced in **estrogen** primed, ovariectomized guinea pigs by progesterone (I). Deoxycorticosterone acetate was about 1/4 as active as I; compound A acetate, about 1/8; 11-ketoprogesterone, 11β-hydroxyprogesterone, and corticosterone about 1/40; compound S, hydrocortisone, cortisone, 17α-hydroxyprogesterone, and 21-deoxyhydrocortisone were ineffective or had only slight activity. The adrenal androgens, adrenosterone and 4-androstene-3,17-dione, and the **amorphous** fraction did not produce the reflex.

L8 ANSWER 16 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1951:21903 CAPLUS

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DOCUMENT NUMBER: 45:21903
ORIGINAL REFERENCE NO.: 45:3878e-g
TITLE: Aralkylammonium steroid sulfates
INVENTOR(S): Grant, Gordon A.; Glen, Wm. L.; Barber, Richard J.
PATENT ASSIGNEE(S): Ayerst, McKenna, & Harrison, Ltd.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2534121		19501212	US 1950-163098	19500519

AB Salts prepared from steroid monosulfates and PhCH2CH(NH2)Me (I) posess central stimulating effects and are useful in **estrogen** therapy. Addition of I sulfate 0.23 g. in 5 ml. distilled H2O to Na estrone sulfate 0.39 in 6 H2O gave an immediate precipitate of I estrone sulfate (II). Extraction of the chilled reaction mixture with CHCl3 and removal of solvent at 35° gave, after vacuum-drying over P2O5, **amorphous** white II, m. 86-8°, containing 54% estrone by the Marrian-Kober test. The N-Me derivative of II, an amorph. white powder, was similarly prepared with PhCH2CH(NHMe)Me sulfate in place of I sulfate. Addnl. 1-phenylpropyl-2-ammonium sulfates prepared were: equilenin, equilin, m. 80-95°, trans-dehydroisoandrosterone, pregnenolone, and estradiol.

L8 ANSWER 17 OF 17 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1931:27393 CAPLUS
DOCUMENT NUMBER: 25:27393
ORIGINAL REFERENCE NO.: 25:3049h-i,3050a
TITLE: The unsaponifiable portion of the bile lipoids
AUTHOR(S): Haussler, E. P.; Brauchli, E.
SOURCE: Helvetica Chimica Acta (1930), 13, 908-15
CODEN: HCACAV; ISSN: 0018-019X
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

AB In an investigation of the estrus hormone, 3 compds. (I, II and III) were isolated from ox bile by repeated extns. and crystns. They were all colorless, insol. in water and KOH, contained neither N nor S, were not precipitated by digitonin, dissolved in CHCl3, did not add Br2 and were not decomposed by KMnO4 in acid. They differed from cholesterol (IV) in their reaction to the Liebermann-Burchard and the Salkowski tests and they gave neg. results in the Rosenheim, Tortelli-Jaffe, Carr and Price, and Pettenkofer tests. None of the 3 acted as an **estrogen** when injected into castrated rats. I (C26H42O4 or C27H44O4) occurs as an addition compound (V) m. 172-3°, [α]D20 (4.7% in CHCl3) -32.5°, with IV. The IV was precipitated with digitonin and I, m. 185-7°, was obtained from the mother liquor. Acetylation of V gave no identifiable product but benzoylation in C5H5N gave a resinous substance, soluble with difficulty in EtOH; it yielded I, m. 194-5°. This I gave an Ac derivative m. 169-70°. II crystallized out during the crystallization of I. It m. 217-8° and reacts with Ac2O but the reaction product could not be isolated. III was obtained at the same time as an **amorphous** powder which yielded crystals m. 255-7°. III appears to have 2OH groups and its Ac derivative m. 231-2°, [α]D20 (1% in PhH) -51°.

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FILE 'CAPLUS' ENTERED AT 18:11:53 ON 27 APR 2006

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L1         15570 S ESTRONE
L2             0 S PIPERATE SALT
L3             0 S PIPERATE ADJ SALT
L4         76430 S ESTROGEN
L5        111337 S STEROIDS
L6            44 S L1 AND AMORPHOUS
L7             0 S L1 AND NON CRYSTALLINE
L8            17 S L4 AND AMORPHOUS
L9           488 S L5 AND AMORPHOUS
L10            0 S L5 AND HORMONE HRT
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=> d l6 1-44 ibib hitstr abs

L6 ANSWER 1 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:21738 CAPLUS
DOCUMENT NUMBER: 130:78450
TITLE: Immunoassay sensor comprising **amorphous** fluoro-polymer-treated optical fiber
INVENTOR(S): Erb, Judith; Downward, James, IV
PATENT ASSIGNEE(S): USA
SOURCE: U.S., 14 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5854863	A	19981229	US 1996-616576	19960315
US 5952035	A	19990914	US 1997-864244	19970528

PRIORITY APPLN. INFO.: US 1996-616576 A3 19960315

AB A biol. sensor having a beam/light shaper which is adapted to inject light into the sensor at substantially the critical angle with respect to the side surface of the sensor. The sensor, of the preferred embodiment of the invention, further may undergo a surface treatment which reduces/eliminates non-specific binding to the sensor surface and a treatment process to reduce light energy losses occurring by mounting and/or inserting the fiber portion of the sensor into the medium of interest. Both the light injection and surface treatment methodologies have utility apart from the biol. immunoassay sensor embodiment described and claimed in this Application and may be independently applied to a biol. sensor. The optical fiber of the biosensor is treated with **amorphous** copolymer, such as perfluoro-(2,2-dimethyl-1,3-dioxole) and tetrafluoroethylene, or coated with Teflon AF. The biosensor is used for immunoassay of antigen, antibody, or antigen-antibody immunocomplex, and is especially useful for detecting female reproductive hormone metabolites such as **estrone**-3-glucuronide and pregnanediol glucuronide.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1997:404918 CAPLUS
DOCUMENT NUMBER: 127:99741
TITLE: Synthesis of starch-based drug carrier for the controlled release of **estrone** hormone

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AUTHOR(S): Won, Chee-Youb; Chu, Chin-Chang; Yu, Tarng-Jenn
CORPORATE SOURCE: Department of Textiles and Apparel, Fiber and Polymer Science Program, Cornell University, Ithaca, NY, 14853-4401, USA
SOURCE: Carbohydrate Polymers (1997), 32(3/4), 239-244
CODEN: CAPOD8; ISSN: 0144-8617
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The objective of this study was to provide new synthetic route to prepare starch as a potential carrier for controlled release of drugs. A starch was modified with bromoacetyl bromide in order to provide more reactive sites for coupling of bioactive **estrone** and a suitable spacer between the drug carrier and the hormone. The degree of substitution/anhydroglucose (AHG) unit was calculated from the bromine content and ranged from 0.11 to 2.29, depending on the ratio of bromoacetyl bromide to starch. The starch-**estrone** conjugate was then synthesized by reacting bromoacetylated starch with the sodium salt of **estrone**. The structures of bromoacetylated starch and starch-**estrone** conjugate were determined by means of FTIR, 1H NMR, 13C NMR and UV. Addnl., x-ray diffraction patterns showed the **amorphous** character of the bromoacetylated starches.

L6 ANSWER 3 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:295218 CAPLUS
DOCUMENT NUMBER: 124:328297
TITLE: **Amorphous**-crystal transition of organic dye assemblies 2: thermal properties of steroids used in rewritable color recording media
AUTHOR(S): Naito, Katsuyuki
CORPORATE SOURCE: Adv. Res. Lab., Toshiba Corp., Kawasaki, 210, Japan
SOURCE: Molecular Crystals and Liquid Crystals Science and Technology, Section A: Molecular Crystals and Liquid Crystals (1996), 277, 473-477
CODEN: MCLCE9; ISSN: 1058-725X
PUBLISHER: Gordon & Breach
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The relationship between mol. structures and **amorphous** thermal properties of some steroids were investigated in the design of rewritable color recording media. **Amorphous** states with a high glass transition temperature (Tg) were produced from steroids with plural hydrogen-bonding sites separated Rapid crystallization was observed for steroids with a hydrogen-bonding site or without a flexible alkyl chain. Polymorphism of crystals is also discussed.

L6 ANSWER 4 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1984:504439 CAPLUS
DOCUMENT NUMBER: 101:104439
TITLE: Intercellular junctions between macrophages in the regional lymph node of the rat after injection of large doses of steroids
AUTHOR(S): Miyata, Kenji; Takaya, Kenichi
CORPORATE SOURCE: Fac. Med., Toyama Med. Pharm. Univ., Toyama, 930-01, Japan
SOURCE: Cell & Tissue Research (1984), 236(2), 351-5
CODEN: CTSRCS; ISSN: 0302-766X
DOCUMENT TYPE: Journal
LANGUAGE: English

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AB Intercellular junctions were often found between macrophages in sinuses of regional lymph nodes of the rat after injection of large doses of cholesterol [57-88-5], cortisone [53-06-5], and **estrone** [53-16-7] at the footpad. They were identified by subplasmalemmal densities, 20-50 nm in width, beneath the plasma membranes of apposed macrophages. No distinct filamentous structures were visible in those dense regions. Electron-dense **amorphous** materials were lined up at the center of the intercellular space in the junctional regions. Some macrophages form clusters with intercellular junctions. No significant difference in the effect of cholesterol, cortisone, and **estrone** on the number of intercellular junctions between macrophages was found.

L6 ANSWER 5 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1969:78254 CAPLUS
DOCUMENT NUMBER: 70:78254
TITLE: 17-Cyclopropyl steroids
INVENTOR(S): Christiansen, Robert G.; Dean, John W.
PATENT ASSIGNEE(S): Sterling Drug Inc.
SOURCE: S. African, 27 pp.
CODEN: SFXXAB
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
ZA 6702519		19680117		
FR 6938			FR	
GB 1188373			GB	
US 3501462		19700317	US	19660502
PRIORITY APPLN. INFO.:			US	19660502

OTHER SOURCE(S): MARPAT 70:78254
AB 17α-Cyclopropyl-4-androsten-17β-ol-3-one (I) and 17α-cyclopropylestra-4,9-dien-17β-ol-3-one (II), which are orally active progestational agents with marked pituitary-inhibiting activity, were prepared by treating 17-oxo steroids with cyclopropyllithium or a cyclo-propylmagnesium halide or by adding carbene to the 17-vinyl steroids. Thus, a solution of 11.4 g. 3-(pyrrolidyl enamine) of 4-androstene-3,17-dione in 200 ml. tetrahydrofuran was added to a solution prepared from 1.95 g. Li and 15.72 g. bromocyclopropane in 125 ml. anhydrous Et2O, and the mixture refluxed 16 hrs. under N. The product was refluxed with 200 ml. MeOH, 16 g. NaOAc, 20 ml. H2O, and 16 ml. HOAc 4 hrs., concentrated, treated with 200 ml. 2N HCl and 10 ml. concentrated HCl, and extracted with 400 ml. CH2Cl2 to give 5.24 g. I, m. 160.4-61° (MeCN), [α]25D 70.2° (1%, CHCl3); λ 242 mμ (ε 16,700). **Estrone** methyl ether was similarly converted to 17α-cyclopropyl-3-methoxyestra-1,3,5(10)-trien-17β-ol (III), m. 119.2-20.6°, [α]25D 44.3° (1%, CHCl3). A solution of 14.92 g. III in 1.1 l. absolute Et2O was dissolved in 1.4 l. liquid NH3 and treated with 14 g. Li and 320 ml. absolute EtOH to give 11.5 g. 17α-cyclopropyl-3-methoxyestra-2,5(10)-dien-17β-ol (IV), m. 125-30°, [α]25D 94.0°, (1%, CHCl3). To 7.0 g. IV in 50 ml. tetrahydrofuran and 100 ml. MeOH was added a solution of 4.6 g. H2C2O4·2H2O in 35 ml. H2O. After 50 min. at room temperature, dilution with 650 ml. H2O gave 17α-cyclopropylestr-5(10)-en-17β-ol-3-one (V), m. 150-2° (C6H14-EtOAc); [α]25D 156.4° (1%, CHCl3). A solution of 2.0 g. V in 75 ml. dry MeOH was treated with 1 ml. 8% aqueous NaOH at

room temperature 30 min. to give 17α-cyclopropylestr-4-en-17β-ol-3-one (VI), m. 130.8-2.0° (C6H14Et2O) or 145.8-7.2° (C6H14-Et2O), [α]25D 13.7° (1%, CHCl3), λ 241 mμ (ε 17,600). A solution of 6.29 g. VI in 125 ml. tetrahydrofuran was stirred at room temperature with 12.4 g. LiAl(tert-BuO)3H 90 min. to give 17α-cyclopropylestr-4-ene-3β,17β-diol (VII), m. 139.0-155.8° (Me2CO-C6H14), [α]25D 1.4° (1%, CHCl3). Acetylation of 1.0 g. VII with C5H5N and Ac2O gave 3β-acetoxy-17α-cyclopropylestr-4-en-17β-ol monohydrate (VIII), m. 96.0-107.8° (decomposition), [α]25D 43.5° (1%, CHCl3). Reduction of 3.15 g. V with 2.16 g. LiAl(tert-BuO)3H gave 17α-cyclopropylestr-5(10)-ene-3,17β-diol (IX) as a mixture of epimers, m. 127-30°, [α]25D 128.9° (1%, CHCl3). A solution of 6.29 g. V in 150 ml. C5H5N was treated with 6.7 g. C5H6NBr3 (pyridine bromine complex) over 30 min. to give 2.50 g. II, m. 150.5-2.5°, [α]25D -295.8° (1%, CHCl3), λ 218, 306 mμ (ε 5800, 20,700). A mixture of 5.0 g. III and 25 ml. Ac2O was heated 24 hrs. and refluxed 4 hrs. to give 17-cyclopropyl-3-methoxyestra-1,3,5(10),16-tetraene (X), m. 90.6-2.8° (MeCN), [α]25D 108.1° (1%, CHCl3). To a solution of 3.1 g. X in 30 ml. CH2Cl2 at 0° was added 2.05 g. 85% 3-ClC6H4CO2OH in 20 ml. CH2Cl2, and the mixture stirred 1 hr. at 0° to give 1.70 g. 17-cyclopropyl-3-methoxyestra-1,3,5(10)-triene-16,17-diol 16-(3-chlorobenzoate) (XI), m. 191.5-2.5° (MeCN), λ 230, 281, 288 mμ (ε 1260, 2150, 200). A mixture of 5.8 g. XI and 300 ml. absolute EtOH was heated to boiling, treated with 15 ml. 2N NaOH and boiled 30 min. to give 3.60 g. 17-cyclopropyl-3-methoxyestra-1,3,5(10)-triene-16,17-diol (XII), m. 137.0-8.0° (Et2O). To a solution of 12.6 g. VI in 150 ml. dry C6H6 was added 40 ml. Et formate and 6.5 g. NaOMe, 15 ml. Et formate added after 3.5 hrs., and the mixture stirred overnight to give **amorphous** 2-hydroxymethylene-17α-cyclopropylestr-4-en-17β-ol-3-one (XIII), λ 248, 307 mμ (ε 10,400, 4500). To a solution of 4.1 g. XIII in 25 ml. warm HOAc was added a solution of 3.27 g. NaOAc·3H2O and 0.85 g. HONH2·HCl in 5 ml. H2O. After 90 min. at room temperature, decomposition in 1.5 l. cold H2O, and recrystn. from Et2O was obtained 17α-cyclopropyl-17β-hydroxyestr-4-eno[2,3-d]isoxazole (XIV), m. 137-319°, [α]25D -77.4° (1%, CHCl3). Similarly 6.30 g. V gave 2-hydroxymethylene-17α-cyclopropylestr-5(10)-en-17β-ol-3-one (XV), m. 207.0-8.0°. A solution of 3.4 g. XV and 2.5 ml. N2H4·H2O in 50 ml. absolute EtOH was kept at room temperature several hrs. to give 17α-cyclopropyl-17β-hydroxyestr-5(10)-eno[3,2-c]pyrazole (XVI), m. 220-1° (decomposition), [α]25D 94.2° (1%, CHCl3), λ 223 mμ (ε 4750). Similarly XIII was treated with N2H4·H2O to give 17α-cyclopropyl-17β-hydroxyestr-4-eno[3,2-c]pyrazole (XVII), m. 143-8°. In the modified Clauberg assay, when administered i.m. at 0.125 mg./kg. and orally at 2.0 mg./kg., II produced a near maximal endometrial response; near maximal maintenance of pregnancy resulted on administration of 20 mg. II/kg. to ovariectomized female rats. A single oral dose (20 mg.; 5 mg./kg.) of II to mature female rabbits in estrus, 24 hrs. prior to mating, blocked ovulation. Other biol. data are given.

L6 ANSWER 6 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1968:403076 CAPLUS
DOCUMENT NUMBER: 69:3076
TITLE: 7α-Methylestrone and its 3-methyl ether
PATENT ASSIGNEE(S): CIBA Ltd.
SOURCE: Fr., 7 pp.
CODEN: FRXXAK

QAZI

DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 1434172		19660408	FR 1964-999102	19641218
CH 473101			CH	
CH 473102			CH	
CH 473109			CH	
CH 484084			CH	
CH 484085			CH	
CH 487876			CH	
CH 487877			CH	
DE 1443681			DE	
DE 1443682			DE	
DE 1443683			DE	
DE 1443684			DE	
GB 1087317			GB	
NL 6415016			NL	
PRIORITY APPLN. INFO.:			CH	19631224
			CH	19640527

AB The title compds., which have estrogenic activity, can be prepared by known methods, in particular by aromatizing the A ring of a 3-oxo-7α-methyl-17-oxygenated androst-4-ene, by heating at 200-600° with or without a solvent. Thus, 10 g. 2,3-dichloro-5,6-dicyanobenzoquinone was added to a solution of 5 g. 3-oxo-7α-methyl-17β-ace-toxy-19-nor-4-androstene in 250 cc. dioxane and the mixture refluxed for 14 hrs. give 1.70 g. **amorphous** 7α-methylestradiol 17-acetate (I). I was dissolved in 4 cc. dihydropyran and 4 cc. tetrahydrofuran (THF), kept 15 min., and treated with 0.1 cc. POCl3 to give 1.76 g. 3-tetrahydropyranyloxy-7α-methyl-17β-acetoxy-1,3,5(10)-estratriene, which was saponified without purification by dissolving in 100 cc. MeOH, adding 2.94 g. K2CO3 in 10 cc. H2O, and refluxing for 15 hrs. to give 1.52 g. 3-tetrahydro-pyranyloxy-7α-methyl-17β-hydroxy-1,3,5(10)-estratriene (II). II was oxidized with CrO3 in Me2CO to give 1.10 g. 7α-methyl- **estrone** 3-tetrahydropyranyl ether (III), m. 157-9°. III (385 mg.) was suspended in 12 cc. 70% HOAc and heated at 60° for 15 min. to give 293 mg. 7α-methylestrone (IV), m. 230-1° (CH2Cl2-MeOH), [α]20D 147°. IV (2.5 g.) was suspended in 12 cc. MeOH and 8.5 cc. CH2Cl2, cooled to -10° and over a period of 30 min. 1.5 g. NaOH in 3 cc. H2O was added with stirring. During the following 90 min. 3.6 cc. Me2SO4 was added dropwise to the mixture A solution of 1.80 g. NaOH in 4 cc. H2O was added and then over 30 min. an addnl. 3 cc. Me2SO4 to give 2.5 g. 7α-methylestrone 3-methyl ether, m. 161-2°, [α]16D 144°. To a solution of 250 mg. Li in 4.6 g. biphenyl and 25 cc. THF was added 0.55 cc. Ph2CH2 and 1 g. 3-oxo-7α-methyl-17,17-ethylenedioxy-1,4-androstadiene rinsing with 5 cc. THF. The mixture was refluxed for 10 hrs. under N, treated with ice and MeOH and with 2.5 g. NH4Cl, kept 10 min., and extracted with benzene. The benzene residue was dissolved in 30 cc. 90% AcOH and heated for 25 min. at 60-80° under N to give 350 mg. 7α-methylestrone, m. 233-6°.

L6 ANSWER 7 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1966:482518 CAPLUS
DOCUMENT NUMBER: 65:82518
ORIGINAL REFERENCE NO.: 65:15468h,15469a-f
TITLE: 17α-(3-Hydroxy-1-propynyl) or

QAZI

17α-(3-hydroxy-1-propenyl) aromatic steroids
INVENTOR(S): Christiansen, Robert G.
PATENT ASSIGNEE(S): Sterling Drug Inc.
SOURCE: 6 pp.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 3265718		19660809	US 1965-487081	19631205
PRIORITY APPLN. INFO.:			US	19631205

AB The title compds., showing mainly hypocholesteremic and some estrogenic activity, were prepared from the resp. 17-oxo; compds. and alkali metal derivs. in inert, anhydrous solvents. E.g., a mixture of 3.67 g. LiNH2 and 4.48 g. HCC.tplbond.CH2OH in 200 ml. dioxane was refluxed under N 2 hrs., 11.38 g. **estrone** Me ether added, the mixture refluxed an addnl. 2 hrs. and cooled to room temperature, 20 ml. HOAc added, and the mixture kept overnight and worked up to yield 3-methoxy-17α-(3-hydroxy-1-propynyl)-1,3,5(10)-estratrien-17β-ol (I), m. 174.0-5.4°, [α]25D --5.9° (1%, CHCl3). I (3.00 g.), 20 ml. Ac2O, and 20 ml. pyridine was stirred 17 hrs. at room temperature, the mixture added to 400 ml. ice H2O, and the solid product worked up to yield 2.82 g. 3-methoxy-17α-(3-acetoxy-1-propynyl)-1,3,5(10)-estratrien-17β-ol, m. 128.0-9.5°, [α]25D --8.1° (1%, CHCl3). Similarly prepared were the following compds. (m.p. and [α]25D (1%, CHCl3) given): 3-methoxy-17α(3-propionyloxy-1-propynyl)-1,3,5(10)-estratrien -17β-ol, 75.26.8°, --8.1°; 3-methoxy-17-(3'-hydroxy-1'-propynyl)-1,3,5-(10)estratrien-17β-ol 3'-nitrate, 107.0-7.8°, --7.1°; 3-methoxy-17β-(3-formyloxy-1-propynyl)-1,3,5(10)estratrien-17β-ol, 107.68.8°, --6.4°; 3-methoxy-17β-acetoxy-17α-(3-acetoxy-1-propynyl)-1,3,5(10)-estratriene as a yellow-brown glass, --, --19.8°; 17α-(3-hydroxy-1-propynyl) - 1,3,5(10) - estratriene - 3,17β-diol, 218.0-22.0°, -18.4°; 3-heptyloxy-17α-(3-hydroxy-1-propynyl)-1,3,5(10)-estratrien-17β-ol, 139.6-40.4°, --3.5°; 3-cyclopentyloxy-17α(3-hydroxy-1-propynyl)-1,3,5(10) - estratrien-17βol, 190.8-2.0°, 4.2°; 3-allyloxy-17α-(3-hydroxy-1-propynyl)-1,3,5(10)estratrien-17β-ol, 137.0-9.9°, --; 3-methoxy-17α-(3methoxy-1-propynyl)-1,3,5(10)-estratrien-17β-ol, 89.0-91.2°, --7.4°; 3-methoxy-17α-(3-phenoxy-1-propynyl)-1,3,5(10)-estratrien-17β-ol, 103.0-7.0°, --13.1°; 3-methoxy-17α-(3-hydroxy-1-propynyl)-1,3,5(10),6-estratetraen-17β-ol, 168.2-9.0°, -- 300.10°; 3-methoxy-17α-(3-hydroxy-1-propynyl)-1,3,5(10),6,8-estrapentaen-17β-ol, 181.8-3.4°, -- 150.6°; 3-methoxy-1-methyl-17α-(3-hydroxy-1-propynyl)-1,3,5(10)-estratrien - 17β-ol, 135.0-7.0°, 40.5°; 3-methoxy-17α-(3-hydroxy-1-propynyl)-1,3,5(10),9, (11)estratetraen-17β-ol, 167.0-181.8°, 94.0°; 3-methoxy-17α-[3-(3-phenylpropionyloxy)-1-propynyl]-1,3,5(10)-estratrien-17β-ol, 92.6-5.4°, --3.1°; 3-methoxy-17α-(3-benzoyloxy-1-propynyl)-1,3,5(10)-estratrien-17β-ol, 122.0-3.8°, --7.6°; 3-methoxy-17α-[3-(p-methoxybenzoyloxy)-1-propynyl]-1,3,5(10)-estratrien-17β-ol, 142.4-3.4°, --5.4°; 3-methoxy-17α-[3-(p-chlorobenzoyloxy)-1-propynyl] -1,3,5(10)-estratrien-17β-ol,

114.6-16.0°, - 3.2°; 3-methoxy-17α-[3-(p-methylbenzoyloxy)-1-propynyl]-1,3,5(10)-estratrien-17β-ol, 124.6-6.0°, --6.9°; 3-methoxy-17α-[3(p-fluorobenzoyloxy)-1-propynyl]-1,3,5(10)-estratrien-17β-ol, 128.6-31.0°, --6.1°; 3-methoxy-17α-[3-(p-nitrobenzoyloxy)-1-propynyl]-1,3,5(10)-estratrien-17β-ol, 138.5-9.2°, --4.5°; 3-methoxy-17α-[3-(3-pyridylcarbonyloxy)-1-propynyl]-1,3,5(10)-estratrien-17β-ol, 160.0-1.2°, --8.6°; 3-methoxy-17α-(3-trimethylacetoxy-1-propynyl)-1,3,5(10)-estratrien-17β-ol, 112.2-13.6°, --5.1°; 3-methoxy-17α-[3-(p-dimethylaminobenzoyloxy)-1-propynyl]-1,3,5(10)-estratrien-17β-ol, 168.6-9.8°, --7.8°; 3-methoxy-17α-[3-[2-(p-chlorophenoxy)-2-methylpropionyloxy]-1propynyl]-1,3,5(10)-estratrien-17β-ol as an **amorphous** amber glass, --, --5.8°; 3,17β-dimethoxy-17α-(3-methoxy-1-propynyl)-1,3,5(10)-estratriene, 77.8-8.2°, --13.4° (no temperature given); 17α-(3-acetoxy-1-propynyl)-1,3,5(10)-estratriene-3,17β -diol, 163.8-5.0°, --8.1°; 17β-acetoxy-17α-(3-hydroxy-1-propynyl)-3-methoxy-1,3,5(10)-estratriene, 153.8-4.8°, --20.4°. I (7.40 g.) was treated with H and 0.50 g. Pd hydroxide on a Sr carbonate catalyst 8 min. to yield 3-methoxy-17α-(3-hydroxy-cis-1-propenyl)-1,3,5(10)-estratrien-17β-ol, m. 143.8-5.2°, [α]25D 65.0° (1%, CHCl3). I (3.40 g.) was treated with 0.78 g. LiAlH4 in solution at reflux under N 2.5 hrs. and worked up to yield 3-methoxy-17α-(3-hydroxy-trans-1-propenyl)-1,3,5(10)-estratrien-17βol, m. 180.0-1.0°, [α]25D 38.2° (1%, CHCl3). Also prepared were 3-methoxy-17α-(3-acetoxy-cis-1-propenyl)- 1,3,5(10)-estratrien-17β-ol, m. 101.0-3.0°, [α]25D 70.0° (1%, CHCl3), and 3-methoxy-17α-(3-acetoxy-trans-1-propenyl)-1,3,5(10)-estratrien-17β-ol, m. 85.0-7.0°, [α]25D 35.7° (1%, CHCl3).

L6 ANSWER 8 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER:	1966:52268 CAPLUS
DOCUMENT NUMBER:	64:52268
ORIGINAL REFERENCE NO.:	64:9788e-h,9789a-b
TITLE:	Phosphorus derivatives of steroid hormones. IV. Steroid amidophosphates
AUTHOR(S):	Riess, Jean
CORPORATE SOURCE:	Inst. Chim, Strasbourg
SOURCE:	Bulletin de la Societe Chimique de France (1965), (12), 3552-60 CODEN: BSCFAS; ISSN: 0037-8968
DOCUMENT TYPE:	Journal
LANGUAGE:	French
OTHER SOURCE(S):	CASREACT 64:52268

GI For diagram(s), see printed CA Issue.

AB cf. CA 63, 8441d. Morpholinium **estrone** morpholidophosphate (I) and morpholinium dehydroepiandrosterone morpholidophosphate (II) were prepared by aminolysis of the corresponding P1-steroid P2-diphenyl pyrophosphates. I and II as well as morpholidophosphorochloridate (III) are reactive intermediates suitable for condensations. A series of completely esterified morpholidophosphates is described; these derivs. are little reactive. The identification of the various types of morpholidophosphates is discussed; their N.M.R. spectra in CDCl3 permit a differentiation between morpholine groups attached to the P and morpholinium cations. **Estrone** phosphoric acid monohydrate (IV) (368 mg.) in 2 cc. 2N aqueous morpholine (V) treated with 1 g. dicyclohexylcarbodiimide (VI) in 10 cc. tert-BuOH and heated 6 hrs. at 80° yielded **amorphous** C-morpholino-N,N'-

dicyclohexylcarboxamidinium salt (VII) of **estrone** morpholidophosphate (VIII). IV (1.1 g.) in a few cc. dry dioxane treated with 3 cc. Bu3N and evaporated, the residual salt treated in 5 cc. dry dioxane with 0.9 cc. (PhO)2P(O)Cl and 1.35 cc. Bu3N, kept 1 hr. at room temperature, and evaporated, and the crude product treated in 5 cc. dry dioxane 8 hrs. at room temperature with 5 cc. 1:1 V-C5H5N yielded 1.415g. VIIIa, m. 155-7° (MeOH-Me2CO). Dehydroepiandrosterone phosphoric acid (1 millimole) gave similarly 350 mg. II, m. 169-73° (Me2CO). V (1 cc.), 1 g. VI, and 10 cc. tert-BuOH heated 8 hrs. at 80° gave 1.180 g. C-morpholino-N,N'-dicyclohexyicarboxamidine (IX). I (102 mg.) in a little MeOH treated with 59 mg. IX gave VII. **Estrone** (2.7 g.) in 10 cc. dry C5H5N added dropwise to 1.8 cc. POCl3 in 10 cc. C5H5N at 0° with stirring and then with 10 cc. dry V and kept 1 hr. yielded 2.53 g. **estrone** dimorpholidophosphate, m. 146-7° (CH2Cl2Et2O). Dehydroepiandrosterone (1.15 g.) in 10 cc. dry dioxane treated with 1 cc. Et3N, added dropwise with stirring to 1 cc. POCl3 in 10 cc. dioxane at 0° during 20 min., kept 1 hr., filtered, treated with 2 cc. V, and kept 1 hr. yielded 1.55 g. dehydroepiandrosterone morpholidophosphorochloridate (X), m. 188-90° (CH2Cl2-Et2O). X (100 mg.) in 5 cc. dioxane and 1 cc. 2N NaOH kept 7 hrs. at 50°, and concentrated to about 1 cc., and treated with 2 cc. 2N HCl gave 75 mg. dehydroepiandrosterone morpholidophosphoric acid (XI) characterized as the Me ester (XII) and as II. XI (40 mg.) in a little CHCl3 and 1 drop V evaporated gave II. X (300 mg.) in 1 cc. C5H5N and 1 cc. absolute MeOH treated after 0.5 hr. with 20 cc. dilute aqueous NaHCO3 and extracted with Et2O gave 245 mg.

XII. X (230 mg.) and 175 mg. dehydroepiandrosterone in 4 cc. dry C5H5N heated 20 hrs. at 80°, and the crude product chromatographed on silica gel plates gave 90 mg. bis(dehydroepiandrosterone) morpholidophosphate. III added to 1 equivalent tributylammonium adenosine phosphate in C5H5N and kept 8 hrs. at 40° gave a major product, Rf 0.74 [iso-PrOH-1% aqueous (NH4)2SO4], containing dehydroepiandrosterone and adenosine, accompanied by P1-dehydroepiandrosterone P2-adenosine pyrophosphate, Rf 0.52, and P1,P2-diadenosine pyrophosphate, Rf 0.17.

L6 ANSWER 9 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1965:454932 CAPLUS
DOCUMENT NUMBER: 63:54932
ORIGINAL REFERENCE NO.: 63:10035c-h,10036a-c
TITLE: Cyano steroids
PATENT ASSIGNEE(S): Shionogi & Co., Ltd.
SOURCE: 28 pp.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 998980		19650721	GB 1963-8396	19630301
JP 40023656		1965	JP	
US 3231566		19660125	US 1963-261215	19630226
PRIORITY APPLN. INFO.:			JP	19620302

AB A new method is described for the direct introduction of a CN group into the β-position of a polycyclic α,β-unsatd. ketone. α-(3-Methoxy-18,19-bisnor-1,3,5(10),13(17)-pregnatetraen-20-one (I) (188 mg.) in 5 ml. tetrahydrofuran (THF) was reacted with 0.43 ml. Et3Al and 0.17 ml. HCN in 5 ml. THF at 20°. Addition of 50 ml. 2N HCl at 10° and extraction with CHCl3 gave 37 mg. dl-3-methoxy-20-oxo-19-nor-

1,3,5(10)-pregnatriene-18-nitrile (II), m. 196-9° (Me2CO-Et2O), λ (95% EtOH) 279, 286 mμ, ν 2246, 1714, 1611, 1579 and 1500 cm-1. Chromatography on alumina of the mother liquors gave II and 15 mg. dl-3-methoxy-20-oxo-19-nor-13ξ,17ξ-1,3,5(10)-pregnatriene-18-nitrile (III), m. 160-4°, λ 280, 286 mμ, ν 2252, 1712, 1610, 1577 and 1500 cm.-1 II was converted into dl-**estrone** 3-methyl ether. Similarly, 11-oxo-8,9-dehydrotigogenin acetate gave 8-cyano-11-oxotigogenin acetate, m. 300-2° (CHCl3MeOH), [α]22D -12.8 ± 2° (CHCl3), ν (Nujol) 2240, 1725 cm-1. Also prepared were 3β-acetyloxy-8-cyano-5α-pregnane-11,20-dione, m. 232-3° (MeOH), [α]24D 97.9 ± 2° (CHCl3); 3β-acetyloxy-11-oxo-5α-22-ergostene-8-carbonitrile, m. 218-220° (CHCl3-MeOH), [α]23D 38.9 ± 2° (CHCl3, ν (Nujol) 2230, 1737, 1720, 1261, 1239 cm.-1; 3,3:17,17-bis(ethylenedioxy)-8-cyano-5-androsten-11-one, m. 199.5-200.5° (Me2CO-Et2O), [α]24D 61.3 ± 2° (CHCl3-Et2O, 99:1), ν (Nujol) 2234, 1712, 1663, 1103, 1092 cm.-1; 17,20:20,21-bis(methylenedioxy)3,3-ethylenedioxy-8-cyano-5-pregnen-11-one, m. 220-3° (CH2Cl2MeOH, 1:1), [α]24D -13.9 ± 2° (CHCl3-Et2O, 99:1), ν 2230, 1716, 1670, 1100 and 1080 cm.-1 A solution of 119 mg. HCN in 7.5 ml. THF was added to 3.78 mg. N-methylsulfonyl-1-methyl-1,2,3,4,4b,5,6,7,9,10-decahydro-1,4a(10aH)-methanoiminomethanophenanthren-7-one in 140 ml. THF at 0° and the mixture left at 20° for 48 hrs. Treatment with 5 g. NaOH in 20 ml. icewater and extraction with CHCl3 gave N-methylsulfonyl-1-methyl-8aβ-cyano- 1,2,3,4,4b,5,6,7,8,8a,9,10-dodecahydro-1,4a(10aH)- methanoiminomethanophenanthren-7-one (IV), m. 223-4° (Me2CO-Et2O), ν 2240, 1720, 1335 and 1150 cm-1. Chromatography of the mother liquor over alumina gave 390 mg. IV and 355 mg. of the -8aα-epimer, m. 209-211°, ν 2238, 1718, 1340, and 1150 cm.-1 A mixture of 1.08 g. HCN in 10 ml. THF and 6.85 g. Et3Al in 40 ml. THF at 0° was added to 3.0 g. dl-2,3,4,4a,5,6,7,8-octahydronaphthalen-2-one in 40 ml. THF and kept at 20° for 1 hr. Addition of 100 ml. N NaOH, and extraction with CHCl3 gave 2.14 g. dl-2-oxo-trans-decahydronaphthalene-8a-carbonitrile (V), m. 568° (Et2O-pentane). Mother liquors gave 1.24 g. **amorphous** substance which on chromatography on 30 g. alumina gave 125 mg. cis isomer, semicarbazone m. 204-7°. Similar reaction of 1.03 g. dl-7α-acetyloxy-2,3,4,4aβ,4bα,5,6,7,8,8aβ,9,10-dodecahydrophenanthren-2-one, 164 mg. HCN, and 1.36 g. Et3Al gave 70 mg. dl-7α-acetyloxy-2-oxotetradecahydrophenanthrene-10aα-carbonitrile (VI), m. 149-151° (Me2CO). The residue from the mother liquors was reacted with 25 ml. (CH2OH)2, 30 mg. pMeC6H4SO2Cl at 120° for 10 min., extracted with CHCl3, the exts. acetylated with 1 ml. Ac2O and 3 ml. pyridine and chromatographed to give the ethylene ketal of VI, m. 167-8° (MeOH-CHCl3) and the 10aβ-epimer, m. 195-202°. Hydrolysis of the ketals with 70% HOAc at 100° for 20 min. gave VI and its 10aβ epimer (VII), m. 190-6°. Addition of 675 mg. HCN in 6 ml. THF to 4.2 g. Et2AlCl in 16 ml. THF at 0° followed by reaction with 1.14 g. dl-1-oxo-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene in 5 ml. THF at 20 for 47 hrs., addition of 40 ml. 2N NaOH solution, and Et2O extraction gave 188 mg. dl-1-oxo-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-4aα-carbonitrile (VIII), m. 150-2°. The **amorphous** residue in 16 ml. EtOH was refluxed with 640 mg. NH2CONHNH2.HCl and 710 mg. anhydrous NaOAc in 4.5 ml. H2O for 2 hrs. to give a semicarbazone (IX), m. 223-8°. IX was refluxed with 60 ml. 2N HCl and 40 ml. C6H6 for 2 hrs., Et2O extracted, the exts. washed with 2N Na2CO3, H2O and saturated NaCl solution and evaporated to give 221 mg. VIII and 31 mg. of the 4aβ epimer, m. 128-30°. Addition

of 1.6 ml. HCN and 500 mg. 7-oxocholesterol acetate to 1.15 g. (iso-PrO)3Al in 20 ml. anhydrous C6H6, reaction for 3 days at 20°, addition of 2N NaOH solution, and extraction with C6H6 gave crude 3,5-cholestadien-7-one (X). Chromatography on 15 mg. alumina and elution with petr. ether-C6H6 (4:1) gave 17 mg. X, m. 112.5-13°, λ (95% EtOH) 200 (ε = 24,100), ν (nujol), 1660, 1620 and 1595 cm.-1 Subsequent eluates with petr. ether-C6H6 (1:1) and C6H6-CHCl3 (4:1) yielded 274 mg. 3β-acetoxy-7-oxo-5α-cholestane-5-carbonitrile, m. 202-4°, [α]20D - 35.1° (CHCl3), ν (nujol) 2237, 1720 and 1243 cm.-1 Eluates with C6H6-CHCl3 (2:1) to CHCl3 gave 3β-hydroxy-7-oxo-5α-cholestane-5-carbonitrile, m. 162-6°. Also prepared were 3β-acetyloxy-20-oxo-5-pregnene-16α-carbonitrile, m. 190-4°; 3,3-ethylenedioxy-17α-hydroxy-11-oxo-D-homo-5-androstene-18-nitrile, m. 237-9°; 3-oxo-5α-cholestane-5-carbonitrile, m. 170-180°; dl-3α-acetyloxy 17-oxo-D-homo-5β-9(11)-androstene-18-nitrile, m. 249-51°.

L6 ANSWER 10 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1965:431898 CAPLUS
DOCUMENT NUMBER: 63:31898
ORIGINAL REFERENCE NO.: 63:5706d-h,5707a
TITLE: Allyl-p-dienones by direct allylation of phenols
AUTHOR(S): Barner, R.; Boller, A.; Borgulya, J.; Herzog, E. G.; v. Philipsborn, W.; v. Planta, C.; Fuerst, A.; Schmid, H.
CORPORATE SOURCE: Univ. Zurich, Switz.
SOURCE: Helvetica Chimica Acta (1965), 48(1), 94-111
CODEN: HCACAV; ISSN: 0018-019X
DOCUMENT TYPE: Journal
LANGUAGE: German

AB The title compds. may be prepared by the interaction of Na p-alkylphenolates and allyl bromide, or from phenol and allyl bromide in the presence of K2CO3. Thus, allyl bromide, 62 g., was added over a period of 1 hr. to a suspension 50 g. p-cresol and 89.2 g. freshly prepared Ag2CO3 in 463 g. H2O at 10-20°, the resulting mixture stirred for 2 hrs. at room temperature, the precipitate filtered off, the aqueous phase extracted with Et2O, the solvent evaporated to a volume of 200 ml., the residue treated with dilute NaOH solution and then washed with H2O, the solvent evaporated and the residue dried to yield 16.3 g. of a mixture of neutral compds. Absorption of the product on a column of alumina and elution with pentane afforded 8% p-tolyl allyl ether, 5% 4-allyl-4-methylcyclohexa-2,5-dien-1-one, b. 35-40°/0.02 mm., n20D 1.5172, 6% 2,4-diallyl-4-methylcyclohexa-2,5-dien-1-one, b. 45-50°/0.02 mm. The reaction of phenol with benzyl chloride under similar conditions as above afforded 4-benzyl-4-methylcyclohexa-2,5-dien-1-one, m. 85-6°, b. 90-100°/0.02 mm., and 2,4-dibenzyl-4-methylcyclohexa-2,5-dien-1-one, b. 125-35°/0.02 mm. 2,4-Bis(γ,γ-dimethylallyl)-4-methylcyclohexa-2,5-dien-1-one, b. 70-75°/0.01 mm., and 4-(γ,γ-dimethylallyl)-4-methylcyclohexa-2,5-dien-1-one, b. 50-55°/0.01 mm., were obtained by adding 5.62 g. γ,γ-dimethylallyl bromide during a period of 0.5 hr. to a solution of 4.0 g. γ-cresol and 2.1 g. KOH in 40 ml. 40% aqueous EtOH at 20%, agitating the mixture for 1.5 hrs., diluting it with H2O and extracting the products with pentane. The isolation was carried on a column of Al2O3 by elution with pentane and pentane/C6H6 mixts. A systematic study revealed that higher yields of p-dienones are obtained with higher alkylated phenols. 2,4-Diallyl-4,6-dimethylcyclohexa-2,5-dien-1-one was produced in 28% yield from 2,4-dimethyl-6-allylphenol by K2CO3-catalysis. Electron-withdrawing substituents decrease the

reactivity of the phenols: 2,4-diallyl-4-methyl-6-bromocyclohexa-2,5-dien-1-one, b. 70-80°/0.02 mm., was formed from 2-bromo-4-methyl-6-allylphenol in only 2.6% yield. 2,6-Dichlorophenol gave no O-dienone. The isolation of 10-allyl-2-oxo-Δ1(9),3-hexahydronaphthalene, m. 49.5-50.5°, and of 3,10-diallyl-2-oxo-Δ1(9),3-hexahydronaphthalene from the reaction of 5,6,7,8-tetrahydronaphthol-2 with allyl bromide in the presence of K2CO3 proved that phenols of condensed aromatic systems may be alkylated in the angular position. All structural assignments are based on the anal. composition and on the proton resonance spectra of the dienones. All data are tabulated. The application of the allylation method of the phenolates to steroids with aromatic rings such as **estrone** and estradiol gave under dearomatization of the ring A the corresponding 10-allyl steroids: 19-vinylandrosta-1,4-diene-3,17-dione, m. 101-3° (7% yield), from **estrone**; 19-vinylandrosta-1,4-dien-3-one, m. 159-60° (6%), and 19-vinylandrosta-1,4-dien-3-one-17βdiol, **amorphous** (3%), from estradiol; 19-vinyl-17-α-methylandrosta-1,4-dien-3-on-17β-ol, **amorphous** (4.5%), and 19-vinyl-17α-ethynylandrosta-1,4-dien-3-on-17β-ol, m. 176-8° (11%), from 17alpha;-methylestradiol and 17α-ethynylestradiol. The γ,γ-dimethylallylation of estradiol gave 19-(β,β-dimethylvinyl)-androsta-1,4-dien-3-on-17β-ol, m. 136-8° (7.2%).

L6 ANSWER 11 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1963:441933 CAPLUS
DOCUMENT NUMBER: 59:41933
ORIGINAL REFERENCE NO.: 59:7609h,7610a-h,7611a-g
TITLE: 17α-Chloroethynyl steroids
INVENTOR(S): Petrow, Vladimir; Burgess, Colin M.; Feather, Peter
PATENT ASSIGNEE(S): British Drug Houses Ltd.
SOURCE: 18 pp.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 919565		19630227	GB 1960-27179	19600804
PRIORITY APPLN. INFO.:			GB	19600804

GI For diagram(s), see printed CA Issue.
AB The 17α-chloroethynyl-17β-hydroxy derivs. of perhydrocyclopentenophenanthrene were prepared and have hormonal activity. trans-Dichloroethylene (20 g.) in 50 ml. Et2O treated with MeLi (from 57 g. MeI and 5.55 g. Li) in 0.5 hr., the mixture left 1.5 hrs., and the Li chloroacetylide (I) refluxed 1.5 hrs. with 14.4 g. dehydroepiandrosterone in 300 ml. PhMe gave 17α-chloroethynyl-5-androstene-3β,17β-diol (Ia), m. 201.5°, [α]25.5D -126° (c 0.637, CHCl3). 6-Methyldehydroepiandrosterone (7.4 g.) in 175 ml. PhMe refluxed 3 hrs. with I (from 2.8 g. Li) gave 17α-chloroethynyl-6-methyl-5-androstene-3β,17β-diol, m. 179-81°, [α]24.5D -104.4°. 6α-Methyl-4-androstene-3,17-dione (6 g.) in 29 ml. dioxane left 0.5 hr. with 7.25 ml. Et orthoformate and 5 drops concentrated H2SO4 gave 3-Et enol ether of 6α-methyl-4-androstene-3,17-dione (II), m. 137-8°. II (8.7 g.) in 90 ml. PhMe treated with I gave 17α-chloroethynyl-6α-methyl-4-androsten-17β-ol-3-one, m. 152.5°, [α]24.5D 8.3° (c 0.252, CHCl3). 4-Methyltestosterone acetate (7 g.), 0.35 g. p-MeC6H4SO3H.H2O, and 210 ml. (CH2OH)2 slowly distilled 2 hrs. (0.5 mm.) gave the 3-ketal (III) of 4-methyltestosterone acetate, m.

177-9°. Saponification of 9.5 g. III with KOH in MeOH-H2O gave the 3-ketal (IV) of 4-methyltestosterone, m. 185-7°. Oxidation of 5.6 g. IV with CrO3-C5H5N overnight gave the 3-ketal (V) of 4-methyl-4-androstene-3,17-dione, m. 210 12°. V (1.98 g.) refluxed 2 hrs. with I gave 17α-chloroethynyl-4-methyl-4-androsten-17β-ol-3one (Va), m. 198-200°, [α]25.6D 22°. Estra-2,5(10)-dien-3-ol-17-one 3-Me ether (1.48 g.) treated as above with I gave 17α-chloroethynyl-3-methoxyestra-2,5(10)-dien-17β-ol (VI), m. 126-7°, [α]28D 68.2°. VI (0.41 g.) in 22 ml. MeOH warmed 15 min. at 60° with 13.2 ml. 3N HCl gave 17α-chloroethynyl-19-nor-4-androsten-17β-ol-3-one, m. 194-4.5°, [α]25.5D -41°. VI (1.04 g.) in 250 ml. MeOH left 1 hr. at room temperature with 0.78 g. anhydrous (CO2H)2 in 15 ml. H2O gave 17α-chloroethynylestr-5(10)-en-17β-ol-3-one (VIa), [α]27D 98.3°. 4-Androsten-17-one (1.37 g.) treated with I as above gave 17α-chloroethynyl-4-androsten-17β-ol, m. 120.5-21.0°, [α]25D 11.2°. **Estrone** (2.7 g.) treated with I gave 17α-chloroethynylestra-1,3,5(10)-triene-3,17β-diol (VII), m. 190.5-91.0°, [α]30D-15°. **Estrone** 3-Me ether and I similarly gave 17α-chloroethynyl-3-methoxyestra-1,3,5(10)-trien-17β-ol, m. 166.5°, [α]25.5D -13.8°. 3-Ethoxyandrosta-3,5-diene-11,17-dione and I gave 17α-chloroethynylandrost-4-en-17β-ol-3,11,17-dione, m. 211-11.5°. **Estrone** (2 g.) in tetrahydrofuran left 3 hrs. with 2 ml. 2,3-dihydropyran gave the 3-tetrahydropyranyl ether (VIII) of **estrone**, m. 147-9°. VIII treated with I gave VII. Androsta-3,5-dien-17-one treated with I in PhMe gave 17α-chloroethynyl-17β-hydroxyandrosta-3,5-diene, m. 164-6°, [α]27D -272°. 1-Hydroxy-4-methylestra-1,3,5(10)-trien-17-one and I gave 17α-chloroethynyl-4-methylestra-1,3,5(10)-triene, 1,17β-diol, m. 215-15.5°, [α]27D 44.5°. 17β-Acetoxy-4-methyl-1,4-androstadien-3-one (2 g.), 2 g. LiAlH4, and 300 ml. Et2O refluxed 45 min. gave 1,4-dimethylestra-1,3,5(10)-trien-17β-ol (IX), m. 78-80°. IX (0.7 g.) oxidized with CrO3 in H2SO4 gave 1,4-dimethylestra-1,3,5(10)-trien-17-one (X), m. 126-8°, [α]24.5D 245°. X with I afforded 17α-chloroethynyl-1,4-dimethylestra-1,3,5(10)-trien-17β-ol, an **amorphous** solid. 17β-Acetoxy-2α methylandrosta-1,4-dien-3-one (5 g.) reduced with 10 g. LiAlH4 in Et2O gave 2,4-dimethylestra-1,3,5(10)-trien-17β-ol (XI), m. 131-2°, [α]26D 71°. XI (2 g.) oxidized with CrO3 gave 2,4-dimethylestra-1,3,5(10)-trien-17-one (XII), m. 188-91°, [α]26D 148°. XII treated with I as above gave 17α-chloroethynyl-2,4-dimethytestra-1,3,5(10)-trien-17β-ol (XIIa), m. 91.5-92.5°, [α]26D -30°. 5β-Methylestra-9(10)-ene-3β,6β-diol-17-one diacetate and I gave 5β-methyl-17α-chloroethynylestra-9(10)-ene-3β,5β,17β-triol. m. 173-4°, [α]26D 147°. 3-Methoxyestra-2,5(10)-dien-17-one and I gave 17α-chloroethynyl-3-methoxy-19-norandrosta-3,5-dien-17β-ol, m. 122-3°, [α]28D -227°. 17β-Acetoxy-2α-methylandrost-4-en-3-one (10 g.) in 10 ml. (CH2SH)2 kept 10 min. at room temperature with 10 ml. BF3.Et2O gave 17β-acetoxy-2α-methyl-4-androstene (XIII), m. 114-15°, [α]26D 62°. XIII (5 g.) in 30 ml. MeOH and 10 ml. H2O containing 2 g. NaOH refluxed 1 hr. and the product oxidized with CrO3 gave 2α-methyl-4-androsten-17-one (XIV), m. 103-4°, [α]26D 156°. XIV treated with I gave 17α-chloroethynyl-2α-methyl-4-androsten-17β-ol, [α]D -10°. 3-Ethoxyandrosta-3,5-dien-17-one and I gave 17α-chloroethynyltestosterone, m. 183.5-84.5°, [α]25.5D

9.0°. Androstenedione enol Me ether (13.05 g.) and H in 0.4 l. EtOAc, 100 ml. alc., and 0.3 ml. C5H5N over Pd-BaSO4 gave 12 g. 3-methoxy-5α-androst-2-en-17-one (XV), m. 96-8°. XV treated with I and the crude product chromatographed on Al2O3 gave 17α-chloroethynyl-5α-androstan-17β-ol-3-one, m. 206.5°, [α]26D -19°. 17β-Acetoxy-4α-methyl-5α-androstan-3-one (5 g.), 15 ml. dioxane, 5 ml. Me orthoformate, and 5 ml. p-MeC6H4SO3H stirred 0.5 hr. at room temperature gave 17β-acetoxy-3-methoxy-4α-methyl-5α-androst-2-ene (XVI), m. 145-7°. XVI on hydrolysis gave 3-methoxy-4α-methyl-5α-androst-2-en-17β-ol (XVII), m. 173-5°. XVII treated with CrO3.C5H5N gave 3-methoxy-4α-methyl-5α-androst-2-en-17-one (XVIII), m. 180-2°. XVIII with I gave after hydrolysis 17α-chloroethynyl-17β-hydroxy-4α-methyl-Sα-androstan-3-one, m. 206-6.5°, [α]26D -35°. Estra-1,3,5(10)-trien-17-one treated with I and the product chromatographed on Al2O3 gave 17α-chloroethynylestra-1,3,5(10)-trien-17β-ol, m. 59-60°, [α]25D -17°. 11β-Hydroxy-4-androstene-3,17-dione (19 g.) and 4 g. p-MeC6H4SO3H in 900 ml. HCO2H left 24 hrs. at room temperature gave 11β-formyloxyandrost-4-ene-3,17-dione (XIX), m. 134-6°, [α]D 203°. XIX (18 g.) in 180 ml. dioxane treated 2 hrs. at room temperature with 900 mg. p-MeC6H4SO3H and 18 ml. Me orthoformate in 5 drops MeOH gave 3-methoxy-11β-formyloxyandrosta-3,5-dien-17-one (XX). XX (18 g.) refluxed 1 hr. with MeOH-KOH gave 3-methoxy-11β-hydroxyandrosta-3,5-dien-17-one (XXI), m. 184-7°, [α]D -73°. XXI treated with I gave 3-methoxy-17α-chloroethynyl-11β,17β-dihydroxyandrosta-3,5-diene (XXII). Crude XXII in MeOH treated 20 hrs. at room temperature with oxalic acid in H2O and the product chromatographed on Al2O3 gave 17α-chloroethynyl-11β,17β-dihydroxyandrost-4-en-3-one, m. 205-5.5° (decomposition), [α]D 40°. 4-Methylestra-1,3,5(10)-trien-17-one and I gave 4-methyl-17α-chloroethynylestra-1,3,5(10)-trien-17β-ol, m. 132-2.5°, [α]26D -18.5°. 6α-Methyl-19-norandrost-4-ene-3,17-dione (3 g.), 30 ml. dioxane, 3 ml. Me orthoformate, and 1 ml. MeOH stirred 45 min. with 0.15 g. p-MeC6H4SO3H gave 3-methoxy-6-methyl-19-norandrosta-3,5-dien-17-one (XXIII), m. 153-5°, [α]26D -145°. XXIII and I gave 17α-chloroethynyl-6-methyl-3-methoxy-19-norandrosta-3,5-dien-17β-ol (XXIV), m. 160-1° [α]26D -260°. XXIV ((0.8 g.) refluxed 1 hr. with 1.8 g. (CO2H)2 in MeOH and H2O gave 17α-chloroethynyl-6α-methyl-19-nortestosterone, m. 165-6°, [α]27D -76.7°. 4-Methyltestosterone (20.8 g.), 200 ml. diethylene glycol, 20 g. KOH, and 20 ml. 100% N2H4.H2O heated 1 hr. to 200°, then kept 2 hrs. at 200°, and the product crystallized gave 4-methyl-5ξ-androst-3-en-17β-ol (XXV), m. 116-18°. XXV (0.5 g.) in 10 ml. Me2CO treated 10 min. with CrO3-H2SO4 gave 4-methyl-5ξ-androst-3-en-17-one (XXVI), m. 141-3°. XXVI treated with I and the product chromatographed on Al2O3 gave 17α-chloroethynyl-4-methyl-5ξ-androst-3-en-17β-ol, m. 131.5°, [α]26D -52°. 19-Norandrost-4-en-17-one and I gave 17α-chloroethynyl-19-norandrost-4-en-17β-ol, m. 84°, [α]27D 59.2°. 3β,5α,6β-Trihydroxyandrostan-17-one (4 g.) in 500 ml. tetrahydrofuran treated with I gave 17α-chloroethynylandrostane-3β,5α,6α,17.beta.-tetrol, [α]22D -55°. 5α,6α-Epoxy-3β-hydroxyandrostan-17-one and I gave 17α-chloroethynyl-3β,17β-dihydroxy-5α,6α-epoxyandrostane, m. 21.8.5°, [α}27D -117°. 5β,6β-Epoxy-3-hydroxyandrostan-17-one and I similarly afforded 17α-chloroethynyl-3β,17β-dihydroxy-5β,6β-epoxyandrostane, m.

200-3°, [α]24D -58°. Androst-4-ene-3,17-dione-3-ethylene mercaptole and I gave 17α-chlorethynyltestosterone. 6α-Methyltestosterone acetate treated with LiMe in NH3 gave 6α-methyl-5α-androstan-17β-ol-3-one acetate, and saponification gave the free alc. The crude material treated with CrO3 gave 6α-methyl-5α-androstane-3,17-dione (XXVII), m. 138-40°. XXVII (1.5 g.) suspended in MeOH left 3 min. with 100 mg. (CO2H)2 gave 3,3-dimethoxy-6α-methyl-5α-androstan-17-one (XXVIII), m. 122-5°. XXVIII treated with I gave 17α-chloroethynyl-17β-hydroxy-6α-methyl-5α-androstan-3-one, m. 201.5-202.5° (decomposition), [α]26D -5.2°.

L6 ANSWER 12 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1963:73516 CAPLUS
DOCUMENT NUMBER: 58:73516
ORIGINAL REFERENCE NO.: 58:12615b-h,12616b-h,12617a-h,12618a-c
TITLE: Steroids and sex hormones. CCXXVII. Fragmentation of monovalent alcohols with lead tetraacetate
AUTHOR(S): Amorosa, M.; Caglioti, L.; Cainelli, G.; Immer, H.; Keller, J.; Wehrli, H.; Mihailovic, M. Lj.; Schaffner, K.; Arigoni, D.; Jeger, O.
CORPORATE SOURCE: Eidg. Tech. Hochschule, Zuerich, Switz.
SOURCE: Helvetica Chimica Acta (1962), 45, 2674-98
CODEN: HCACAV; ISSN: 0018-019X
DOCUMENT TYPE: Journal
LANGUAGE: German
OTHER SOURCE(S): CASREACT 58:73516

AB cf. ibid. 2420; CA 57, 8627g. The fragmentation of monohydric alcs. with Pb(OAc)4 (I) was extended and the results were correlated on the basis of the new exptl. evidence. The fragmentation process is critically influenced by the choice of the solvent and is independent from sterical factors. The available evidence is interpreted on the basis of a general scheme involving the participation of oxygen and carbon radicals. The practical value of the reaction is illustrated by the straightforward partial synthesis of several steroid and triterpene derivs. otherwise available only by more elaborate multi-step procedures. 3,3-Ethylenedioxy-17α-acetoxy-5-androstene (1.48 g.) in 30 cc. 10% KOH-MeOH refluxed 1 hr. gave 1.3 g. crystalline 3,3-ethylenedioxy-17α-hydroxyandrost-5-ene (II), m. 154° (Me2CO-hexane), [α]D -52° (c 1.18) (all rotations were measured in CHCl3 except where stated otherwise). 3-Oxo-17β-acetoxy-13α-androst-4-ene (III) (180 mg.) in 15 cc. dry C6H6 refluxed 14 hrs. with 20 mg. p-MeC6H4SO3H and 2 cc. (CH2OH)2 with the azeotropic removal of H2O, cooled, poured into H2O, and extracted with Et2O gave 200 mg. crude 3,3-ethylenedioxy-17β-acetoxy-13α-androst-5-ene which heated 1 hr. on the water bath in 15 cc. 5% KOH-MeOH and chromatographed on Al2O3 yielded 137 mg. oily 3,3-ethylenedioxy-17β-hydroxy-13α-androst-5-ene (IV), [α]D -46° (c 1.19). 17α-Epimer of III (2.066 g.) in 500 cc. dry C6H6, 10 cc. (CH2OH)2, and 120 mg. p-MeC6H4SO3H refluxed overnight with the azeotropic removal of H2O and poured into H2O, and the crude product chromatographed on Al2O3 yielded 2.0 g. 3,3-ethylenedioxy-17α-acetoxy-13α-androst-5-ene (V), m. 123° (Me2CO-petr. ether). V (1.5 g.) in 50 cc. 5% KOH-MeOH refluxed 1 hr. yielded the 17α-OH analog (VI) of V, m. 137° (Me2CO-hexane), [α]D -101° (c 0.67). 17α-Epimer of II (5 g.), m. 187-8°, refluxed 15 hrs. with stirring with 10 g. I and 1 g. CaCO3 in 250 cc. dry C6H6, filtered, and evaporated, the residual yellow oil (5.6 g.) in 85 cc. EtOH treated with 4.6 g. AgNO3 in 46 cc. H2O and then dropwise with stirring with 4.6 g. NaOH in 185 cc. H2O, stirred 12 hrs., filtered through Celite, concentrated, washed with Et2O to remove 500 mg. oily neutrals,

acidified with cooling with 5% H_2SO_4, and extracted with Et_2O, and the **amorphous** residue from the extract treated with CH_2N_2-Et_2O and chromatographed on Al_2O_3 yielded 2 g. Me 3,3-ethylenedioxy-13,17-secoandrosta-5,12-dien-17-oate (VII), m. 122° (Et_2O-pentane), $[\alpha]D$ -105° (c 1.11), 340 mg. Me 3,3-ethylenedioxy-13-acetoxy-13,17-seco-13ξ-androst-5-en-17-oate (VIII), m. 145° (Me_2CO-hexane), $[\alpha]D$ -18° (c 0.69), and 65 mg. 3,3-ethylenedioxy-17-oxo-17a-oxa-D-homoandrost-5-ene (IX), m. 251-2° (CH_2Cl_2-Me_2CO), $[\alpha]D$ -106° (c 0.74). II (2 g.) treated in the usual manner with I, the resulting mixture after-oxidized with Ag_2O and worked up gave 200 mg. oily neutrals and 1.52 g. **amorphous**, alkali-soluble solid which esterified with CH_2N_2-Et_2O and chromatographed on Al_2O_3 gave 680 mg. crystalline VII, 120 mg. crystalline VIII, and a small of IX (identified in the thin-layer chromatogram with 19:1 C_6H_6-MeOH). Oily IV (780 mg.) treated with I, after-oxidized with Ag_2O, and worked up yielded 100 mg. oily neutrals and 600 mg. alkali-soluble material which esterified with CH_2N_2-Et_2O and chromatographed on Al_2O_3 gave 160 mg. crystalline VII, 52 mg. crystalline VIII, and 45 mg. crystalline IX. VI (1 g.) treated with I, after-oxidized with Ag_2O, and worked up yielded 84 mg. oily neutrals and 1.01 g. alkali-soluble material which esterified with CH_2N_2-Et_2O and chromatographed on Al_2O_3 gave 480 mg. VII, 59 mg. crystalline VIII, and a small amount of IX (identified in the thin-layer chromatogram). VIII (90 mg.) refluxed 2 hrs. with 5 cc. 10% KOH-MeOH, acidified with stirring, and cooling with dilute HCl, and extracted with Et_2O yielded 60 mg. IX, m. 250-2° (CH_2Cl_2-hexane). IX (69 mg.) in 10 cc. AcOH and 5 cc. H_2O heated 1 hr. at 60°, cooled, dissolved in C_6H_6, and worked up, and the crude product chromatographed on the 30-fold amount Al_2O_3 yielded 36 mg. 3,11-dioxo-17a-oxa-D-homoandrost-4-ene, m. 202-3° (Me_2CO-hexane) (sublimed in vacuo at 180°), $[\alpha]D$ 42° (c 1.29). I (5 g.), 1 g. $CaCO_3$, and 150 cc. cyclohexane refluxed 20 min., treated with 1 g. 3β-acetoxy-17β-hydroxy-5α-pregnane, refluxed 7 hrs., filtered, diluted with Et_2O, and worked up, and the oily product (1.15 g.) chromatographed on Al_2O_3 yielded 445 mg. of an oily 3β-acetoxy-17-oxo-13,17-seco-5α-pregnene (X) and 150 mg. crystalline 3β,13ξ-diacetoxy-17-oxo-13,17-seco-5α-pregnane (XI), m. 113-14° (aqueous MeOH), $[\alpha]D$ 9° (c 0.8). X (500 mg.) treated 17 hrs. at room temperature with 5% KOH-MeOH yielded 470 mg. of an **amorphous** 3β-hydroxy-17-oxo-13,17-seco-5α-pregnene (XII); 2,4-dinitrophenylhydrazone m. 193° (CH_2Cl_2-MeOH). XI (47 mg.) treated 20 hrs. with 15 cc. 1% KOH-MeOH gave 43 mg. crystalline 3β-hydroxy- 13ξ-acetoxy-17-oxo-13,17-seco-5α-pregnane, m. 143° (aqueous MeOH and CH_2Cl_2-heptane), $[\alpha]D$ 26° (c 0.6). XI (415 mg.) heated 0.5 hr. at 250° under N, and the distillate dissolved in petr. ether and chromatographed on Al_2O_3 yielded 85 mg. oily 3β-acetoxy-17-oxo-13,17-seco-5α-pregn-13(18)ene (XIII), $[\alpha]D$ -70° (c 1.0). XII (100 mg.) in 15 cc. EtOH hydrogenated over 50 mg. 10% Pd-C and then treated with 1:1 Ac_2O-C_5H_5N gave crystalline 3β-acetoxy-17-oxo-13,17-seco-5α,13ξ-pregnane (XIV), m. 90-2° (aqueous MeOH), $[\alpha]D$ - 48° (c 0.6). XIII (15 mg.) in EtOH hydrogenated over 10 mg. 10% Pd-C gave XIV, m. 90-1° (aqueous MeOH). 18α-Oleanolic acid lactone (XV) (4.1 g.) in 300 cc. dry C_6H_6 refluxed 16 hrs. with 1.6 g. $CaCO_3$ and 13 g. dry I, filtered through Celite, and worked up, and the crude product chromatographed on the 30-fold amount Al_2O_3 yielded 89 mg. crystalline acetate of XV, m. 354-5°, and 431 mg. XVI (R = CHO)(XVII), m. 239-40° (Me_2CO-petr. ether), $[\alpha]D$ 51° (c 0.82); 2,4-dinitrophenylhydrazone m. 248-9° (CH_2Cl_2-MeOH). XVII (54 mg.) in 15 cc. dioxane refluxed 4 hrs. with 200 mg. $NaBH_4$, and the crude product heated 6 hrs. at 80°

with 5 cc. 1:1 Ac2O-C5H5N gave 57 mg. crystalline XVI (R = CH2OAc) (XVIII), m. 189-91° (aqueous MeOH), [α]D41° (c 0.6). XV (2.19 g.) oxidized with I, and the crude product reduced with NaBH4 and acetylated gave 382 mg. XVIII. XVIII (71 mg.) and 90 mg. KOH in 6 cc. MeOH kept 17 hrs. at room temperature and extracted with Et2O yielded nearly 100% XVI (R = CH2OH) (XIX), m. 208-9° (CH2Cl2-heptane), [α]D 46° (c 0.5). XVIII (67 mg.) in 10 cc. AcOH hydrogenated 2 hrs. under ambient conditions over 50 mg. prehydrogenated PtO2 yielded XX (R = CH2OAc) (XXI), m. 150-2° (aqueous MeOH), [α]D 25° (c 0.5). XIX (250 mg.) in 20 cc. AcOH hydrogenated similarly gave XX (R = CH2OH) (XXII), m. 208-10° (aqueous MeOH), [α]D 19° (c 0.6). XXII (200 mg.) in 10 cc. Me2CO oxidized with 3 cc. Kiliani solution during 15 min. at room temperature, diluted with 10 cc. MeOH, poured into H2O, and extracted with Et2O, and worked up with the removal of the neutrals, and the acidic product (23 mg.) esterified with CH2N2-Et2O yielded XX (RCO2Me), m. 207-8° (aqueous MeOH), [α]D 13° (c 0.5). XVIII (158 mg.) in 5cc. dry Et2O and 5 cc. dry C5H5N treated 6 days at room temperature with 175 mg. OsO4 and then with H2S and extracted with Et2O, the extract washed with dilute HCl and H2O and evaporated, the residue (206 mg.) in 30 cc. MeOH and 8 cc. C5H5N treated 0.5 hr. with 1.3 g. HIO4 in 6 cc. H2O, and the crude product (120 mg.) chromatographed on Al2O3 yielded 54 mg. XXIII, m. 184-6° (CH2Cl2-heptane). 3-Oxo-17β-acetoxy-4,4-dimethyl-5-androstene (2 g.) in 500 cc. 90% MeOH stirred 45 min. at room temperature with 2 g. NaBH4 and extracted with Et2O gave 1.903 g. 3β-hydroxy-17β-acetoxy-4,4-dimethyl-5-androstene (XXIV), m. 198-9° (Me2CO-hexane), [α]D -----91° (c 0.9). Dry I (6 g.) and 800 mg. CaCO3 in 180 cc. dry C6H6 refluxed briefly, treated with 2.017 g. XXIV, refluxed overnight with stirring, cooled, filtered, poured into H2O, and extracted with Et2O, the residual light yellow oil from the extract (2.359 g.) in 36 cc. EtOH treated with 1.95 g. AgNO3 in 20 cc. H2O and then dropwise with 1.95 g. NaOH in 79 cc. H2O, stirred overnight, filtered through Celite, poured into dilute aqueous NaOH, washed with Et2O to remove 232 mg. oily neutrals, acidified, and extracted with Et2O yielded 528 mg. crystalline 17β-hydroxy-3,4-seco-4,4-dimethylandrosta-4(4'),5-dien-3-oic acid (XXV), m. 204-5° (aqueous MeOH and Me2CO-hexane), [α]D -18° (c 1.1); the neutral material (232 mg.) in 7.5 cc. C5H5N stirred 2.5 hrs. at room temperature with 500 mg. CrO3 in 5 cc. C5H5N diluted with 10 cc. MeOH, and worked up, and the crude product chromatographed on Al2O3 yielded 10 mg. 3,17-dioxo-4,4-dimethyl-5-androstene (XXVI), m. 161-3° (Me2-CO-MeOH). XXIV (1 g.) in 80 cc. AcOH refluxed overnight with 4 g. I and worked up did not yield any aldehyde. 3-Oxo-17β-hydroxy-4,4-dimethylandrost-5-ene (242 mg.) in 6 cc. C5H5N treated 2.5 hrs. at room temperature with 400 mg. CrO3 in 4 cc. C5H5N, and the crude product (213 mg.) chromatographed on Al2O3 gave XXVI, m. 162.5-3.5° (Me2CO-MeOH), [α]D 55° (c 0.7). XXV (257 mg.) in a little Et2O treated 0.5 hr. with CH2N2 and evaporated, the residual oil in 6 cc. C5H5N stirred 2.5 hrs. with 400 CrO3 in 4 cc. C5H5N, treated with 10 cc. MeOH, and worked up, and the crude crystalline product (251 mg.) chromatographed on the 50-fold amount Al2O3 gave 152 mg. Me 17-oxo-3,4-seco-4,4-dimethylandrosta-4(4')-5-dien-3-oate (XXVII), m. 100-1° (petr. ether), [α]D 66° (c 1.1). XXVII (100 mg.) and 200 mg. maleic anhydride in 10 cc. xylene refluxed 36 hrs., and evaporated, and the residue heated in vacuo at 70-80° left the adduct, m. 211-12° (CH2Cl2-petr. ether), [α]D 59° (c 0.95). I (2 g.) and 2 g. CaCO3 in 200 cc. dry C6H6 boiled briefly, cooled, treated with 2 g. 3,17-dioxo-19-hydroxyandrost-4-ene (XXVIII), refluxed 14 hrs., and worked up, and the crude oily product (2.03 g.) chromatographed on

Al2O3 gave 1.210 g. crystalline 3,17-dioxo-10β-acetoxyestr-4-ene (XXIX), m. 195-6° (Me2CO-petr. ether), [α]D 102° (c 0.87), and 572 mg. unchanged XXVIII, m. 164° (Me2CO-petr. ether). XXIX (120 mg.) in 9 cc. Tetraline refluxed 1 hr. and evaporated and the residue chromatographed on Al2O3, gave 85 mg. **estrone** (XXX), m. 250-2° (Me2CO-petr. ether). Crude XXIX gave similarly 71% XXX. XXIX (100 mg.) in 7 cc. AcOH refluxed 0.5 hr. with stirring with 200 mg. Zn dust, filtered, and evaporated, and the residue chromatographed on Al2O3 gave 75 mg. 3,17-dioxoestr-4-ene (XXXI), m. 164° (Me2CO-petr. ether). XXXI (100 mg.) refluxed 5 hrs. with 100 mg. I and 100 mg. CaCO3 in 40 cc. dry C6H6, and the crude crystalline product (90 mg.) chromatographed on Al2O3 yielded only unchanged XXXI. XXIX (98 mg.) in 10 cc. tetrahydrofuran added dropwise at 0° to 200 mg. LiAlH(OBu-tert)3 in 5 cc. tetrahydrofuran, stirred 20 min. at 0% decomposed with 10 cc. 5% aqueous AcOH, and extracted with Et2O yielded 70 mg. 3-oxo-10β-acetoxy-17β-hydroxyestr-4-ene (XXXII), m. 153-6° (Me2CO-petr. ether), [α]D 49° (c 1.10). XXXII (260 mg.) in 10 cc. 1:1 Ac2O-C5H5N kept 12 hrs. at room temperature gave 250 mg. crystalline 17-acetate of XXXII, m. 124-6° (Me2CO-petr. ether), [α]D 29° (c 0.97). XXIX (1.2 g.) and 2.5 g. dichlorodicyano-p-benzoquinone in 100 cc. dioxane refluxed 15 hrs. with stirring, cooled, filtered, and evaporated, and the residue chromatographed on Al2O3 gave 615 mg. 3,17-dioxo-10β-acetoxyestra-1,4-diene (XXXIII), m. about 250° (Me2CO-petr. ether), [α]D 38° (c 1.37). 3-Oxo-10β,17β-diacetoxyestr-4-ene (150 mg.) in 6 cc. tert-BuOH and 0.8 cc. AcOH refluxed 6 hrs. with stirring with 100 mg. SeO2, treated with an addnl. 100 mg. SeO2, heated 0.5 hr., decanted, and evaporated, and the oily residue (165 mg.) chromatographed on Al2O3 gave 46 mg. 3-oxo-10β,17β-diacetoxyestra-1,4-diene (XXXIV), m. 213-15° (aqueous MeOH), [α]D -32° (c 0.87), -30° (c 0.80, dioxane). XXXIII (225 mg.) in 15 cc. tetrahydrofuran stirred 45 min. at 0° with 500 mg. LiAlH(OBu-tert)3 in 15 cc. tetrahydrofuran and worked up, and the crude 3-oxo-10β-acetoxy-17β-hydroxyestra-1,4-diene (220 mg.) treated 48 hrs. with 10 cc. 1:1 Ac2O-C5H5N and chromatographed on Al2O3 yielded 195 mg. XXXIV, m. 215° (repptd. from Me2CO with petr. ether). XXVIII (8.6 g.) in 100 cc. 1:1 Ac2O-C5H5N kept at room temperature overnight and evaporated, the residue in C6H6 filtered through Al2O34 and evaporated, the residual XXX in 500 cc. C6H6 and 50 cc. (CH2OH)2 refluxed 22 hrs. with stirring with 500 mg. p-MeC6H4SO3H with the azeotropic removal of H2O, poured onto ice, and extracted with Et2O, the residual oily acetate of 3,3:17,17-bis(ethylenedioxy)-19-hydroxyandrost-5-ene (XXXV) heated 1 hr. with 400 cc. 5% KOH-MeOH, treated dropwise with H2O, and filtered, and the residue chromatographed on Al2O3 yielded 6.8 g. XXXV, m. 199-200° (Me2CO-petr. ether), [α]D -59° (c 1.20). Dry I (3.25 g.), 3.25 g. CaCO3, and 175 cc. dry C6H6 heated briefly to boiling, cooled, treated with 3.25 g. XXXV, refluxed 6 hrs. with stirring, kept overnight, and worked up gave 3.5 g. oily 6-acetate of 3,3:17,17-bis(ethylenedioxy)6ξ-hydroxyestr-5(10)-ene (XXXVI) which refluxed 1 hr. with 250 cc. 5% KOH-MeOH and chromatographed on Al2O3 gave 2.71 g. XXXVI, m. 157-8° (Me2CO-petr. ether), [α]D 73° (c 0.92). XXXVI (200 mg.) in 40 cc. dry C6H6 and 4 cc. dry Me2CO refluxed 16 hrs. with stirring with 500 mg. (iso-PrO)3Al and worked up, and the crude product (197 mg.) chromatographed on Al2O3 yielded 160 mg. 3,3:17,17-bis(ethylenedioxy)-6-oxo-estr-5(10)-ene (XXXVII) m. 178-80° (Me2CO-petr. ether), [α]D 43° (c 0.94). XXXVII (1 g.) in 10 cc. EtOH, 31 cc. (HOCH2CH2)2O, and 10 cc. N2H4.H2O refluxed 1.5 hrs., cooled, treated with 5 g. ground KOH, refluxed 0.5 hr., treated with 60 cc. (HOCH2CH2)2O, distilled to 190° pot temperature,

refluxed 3.25 hrs., cooled, and worked up, and the crude product (chromatographed on Al2O3 yielded 483 mg. 3,3:17,17-bis(ethylenedioxy)estr-5-ene (XXXVIII), m. 135-7° (Me2CO-petr. ether), [α]D -196° (c 1.49), and 278 mg. unidentified C22H32O5, m. 196-7° (Me2CO-petr. ether), [α]D -59° (c 0.66). XXXVIII (40 mg.) in 6 cc. AcOH and 10 drops H2O refluxed 1 hr. and evaporated, and the residue in Et2O filtered through Al2O3 and evaporated gave XXXI, m. 163-4° (Me2CO-petr. ether). XXXVII (470 mg.) in 15 cc. AcOH, 15 cc. MeOH, and 7 drops H2O heated 1 hr. at 60° and the resulting **amorphous**, crude product (490 mg.) in 1:1 C6H6-Et2O filtered through Al2O3 and evaporated yielded 3,3-ethylenedioxy-6,17-dioxoestr-5(10)-ene (XXXIX), m. 189-90° (Me2CO-petr. ether), [α]D 167° (c 0.63). XXXIX (250 mg.) in 10 cc. AcOH refluxed 1 hr. and evaporated, and the residue chromatographed on Al2O3 yielded 136 mg. crystalline 3,6,17-trioxoestr-5(10)-ene (XL), m. 163° (Me2CO-petr. ether), [α]D219° (c 0.79). XXXVII (500 mg.) in-10 cc. AcOH and 10 drops H2O refluxed 1 hr. and evaporated, and the crude product in CH2Cl2 filtered through Al2O3 and evaporated gave 400mg. XL, m. 163°. Dry I (17 g.), 2 g. CaCO3, and 5.163 g. 3,3:20,20-bis(ethylenedioxy)-21-hydroxypregn-5-ene, in 375 cc. dry C6H6 refluxed 14 hrs. with stirring, filtered through Celite, and worked up, and the crude, oily product (180 mg.) chromatographed in Al2O3 gave 878 crystalline AcOCH2CH2 ester (XVI) of 3,3-ethylenedioxyandrost-5-en-17β-carboxylic acid (XLII), m. 107-8° (Me2CO-petr. ether), [α]D -6° (c 0.92). 3,3-Ethylenedioxy-17β-formylandrost-5-ene (2.0 g.), m. 192-3°, and 1.0 g. KMnO4 in 150 cc. Me2CO treated dropwise during 5 min. with stirring at 16-18° with 10 cc. H2O, stirred 0.5 hr., poured into dilute aqueous NaOH, and worked up gave 1.303 g. crystalline XLII, m. 255-6° (Me2CO-hexane), [α]D -10° (c 1.12). XLII (300 mg.) in 10 cc. MeOH treated with 5.54 cc. 0.155M NaOMe-MeOH and evaporated, the residual Na salt kept 0.5 hr. at room temperature with 10 cc. dry C6H6, 2 cc. (COCl)2, and 4 drops C5H5N, filtered, and evaporated, the residue in 5 cc. C5H5N and 5 cc. C6H6 stirred overnight at room temperature with 2 cc. AcOCH2CH2OH and worked up, and the crude product chromatographed on Al2O3 yielded 49 mg. XLI, m. 108-9° (Me2CO-petr. ether), [α]D -6° (c 0.87), and 108 mg. crystalline 2-HOCH2CH2 ester of XLII which treated 1 hr. at 80° with 1:1 Ac2O-C5H5N yielded XLI.

L6 ANSWER 13 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1963:66699 CAPLUS
DOCUMENT NUMBER: 58:66699
ORIGINAL REFERENCE NO.: 58:11439h,11440a-h
TITLE: Cardiac glycosides. LI. The autoxidation of strophanthidine. 3. Degradation of 10β-hydroxy-19-norperiplogenin to **estrone**
AUTHOR(S): Wartburg, Albert v.
CORPORATE SOURCE: Sandoz Ltd., Basel, Switz.
SOURCE: Helvetica Chimica Acta (1963), 46, 591-601
CODEN: HCACAV; ISSN: 0018-019X
DOCUMENT TYPE: Journal
LANGUAGE: German
OTHER SOURCE(S): CASREACT 58:66699
GI For diagram(s), see printed CA Issue.
AB cf. preceding abstract 10β-Hydroxy-19-norperiplogenin (I), a rearrangement product of strophanthidine, was converted by systematic degradation to 10β-hydroxy-19-norandrostane derivs. and **estrone** (II). The correlation with those steroids of well-known structure confirms the exact position and the β-orientation of the tertiary OH group at C-10 in I. 3-Acetate (5.0 g.) of I oxidized with

KMnO4, in Me2CO as described previously (loc. cit.), and the acid fraction (2.2 g.) methylated with CH2N2 and chromatographed gave 1.0 g. 3β-acetoxy-5,10,14-trihydroxy-17β-carbomethoxy -5β, 14β-estrane (III), m. 154-9° and 177-84°. III (200 mg.) in 3 cc. dry C5H5N treated at -15° with 0.6 cc. SOCl2, refrigerated 20 hrs., poured onto 100 g. crushed ice, and extracted with CHCl3, and the residue from the extract chromatographed on Al2O3 yielded 150 mg. 5,10-cyclosulfite (IV) of III, m. 150-7° (Me2CO), [α]20D 33.7° (c 0.520, CHCl3). III (1.0 g.) in 100 cc. AcOH treated 1 hr. at 10° with dry HCl and evaporated at 25°, and the **amorphous** residue chromatographed on Al2O3 gave 853 mg. 3β-acetoxy-5,10-dihydroxy-17β-carbomethoxy-5β-estr-14-ene (V), m. 168-71° (Et2O), [α]20D 57.6° (c 0.513, CHCl3). V (500 mg.) in 50 cc. AcOH hydrogenated about 40 min. over 140 mg. prehydrogenated PtO2.H2O yielded 400 mg. 5β-estrane analog (VI) of V, m. 128-30° and 150-2°, [α]20D 78.7° (c 0.483, CHCl3). The Grignard derivative From 7.2 g. p-MeOC6H4Br and 1.08 g. Mg in 24 cc. dry tetrahydrofuran treated dropwise with 500 mg. dry VI in 24 cc. dry tetrahydrofuran, the mixture refluxed 5-6 hrs., and worked up gave 2.258 g. yellow oil which, diluted with a little C6H6, precipitated 471 mg. crystalline 17β-(p-MeOC6H4)2(HO)C derivative (VII) of 3β,5,10-trihydroxy-5β-estrane (VIII), m. 280-1° (Me2CO), [α]20D -58.2° (c 0.550, CHCl3); the residue from the mother liquor chromatographed on Al2O3 gave 245 mg. (p-MeOC6H4)2C:CH2, m. 130-2°, and a mixture (1.31 g.) of mainly 3β-acetate of VIII with a little VII; the mixture in 9 cc. MeOH kept overnight with 0.6 g. KOH in 0.6 cc. H2O, diluted with 9 cc. H2O, concentrated in vacuo at 23° to about 8 cc., extracted with 1:2 CHCl3-Et2O, and the oily residue (0.80 g.) from the extract chromatographed gave an addnl. 143 mg. VII. (VII (800 mg.) in 17 cc. AcOH refluxed 75 min. and evaporated gave 800 mg. crude 17-dianisylmethylene analog (VIII) of VII. VIII (800 m.g.) in 125 cc. dry EtOAc ozonized 15 min. at -80°, kept 20 min. at -80°, treated with a stream of N, and evaporated in vacuo at 20% the residue in 20 cc. AcOH reduced with Zn dust and filtered, the filtrate worked up, and the residual yellow lacquer (799 mg.) chromatographed on Al2O3 yielded 400 mg. (p-MeOC6H4)2CO, m. 144-5° (absolute EtOH), 117 mg. oily material (not investigated further), and 171 mg. 3β,5,10β-trihydroxy-19-nor-5β-androstan-17-one (IX), m. 208-12° (Me2CO-Et2O), [α]20D 79.3° (c 0.473, CHCl3). IX (72 mg.) in 3 cc. dry tetrahydrofuran treated with 3 cc. solution of about 250 mg. LiAlH(OBu-tert)3 at 0°, the mixture kept 1 hr. at room temperature and worked up, the resulting crude product (68 mg.) shaken 21 hrs. under N with 45 mg. prehydrogenated PtO2.H2O in 3 cc. H2O and 15 cc. 9:8 Me2CO-H2O, filtered, and evaporated, the residue (67 mg.) refluxed 15 min. in 13 cc. AcOH while being treated with a stream of N, and evaporated, and the crude residue (67 mg.) chromatographed on Al2O3 gave 25 mg. (crude) 10β-hydroxy-19-nortestosterone (X), m. 204-10° (Me2.CO-pentane). Estradiol 3-Me ether reduced with Li in liquid NH3, and the resulting 1,4-dihydroestradiol 3-Me ether cleaved with (CO2H)2 gave 17β-hydroxy-5(10)-estren-3-one which with o-HO2CC6H4CO2OH gave 5β,10β-oxido-19-norandrostan-17-ol-3-one (XI). XI (1 g.) in 160 cc. 5% KOH-MeOH refluxed 1 hr., diluted with 50 cc. H2O, and extracted with Et2O, and the residue from the extract chromatographed on Al2O3 yielded 267 mg. X, m. 208-15° (Me2CO-pentane), [α]20D 76.4° (c 0.465, MeOH). X (100 mg.) in 18 cc. Me2CO and 10 cc. H2O shaken 22 hrs. under O with Pt (from 50 mg. PtO2.H2O in 6 cc. H2O), and the crude product chromatographed on Al2O3 gave 10β-hydroxy-19-nor-4-androsten-3,17-dione (XII), m. 198-211° (EhO), [α]20D 143.0° (c 0.490, CHCl3). IX (70 mg.) in 14 cc. Me2CO and 5 cc. H2O shaken 21 hrs. under O with Pt from 50 mg. PtO2.H2O in 3 cc. H2O, and the crude crystalline product refluxed 15 min. in 5 cc. AcOH while being treated with a stream

of N, evaporated, and chromatographed on Al23 gave 70 mg. (crude) XII, m. 197-207° (Et2O-Me2CO or Et2O), [α]20D 141° (c 0.455, CHCl3). XII (50 mg.) in 6 cc. AcOH treated 2 hrs. at 7° with dry HCl and evaporated at 20°, the residue in Et2O washed with aqueous KHCO3 and H2O and evaporated, and the residue chromatographed on Al2O3 gave 26 mg. II, m. 254-9° (Me2CO); the crystalline residue from the mother liquor with Ac2O-C5H5N gave the acetate of II, m. 125-7°. Testosterone (200 mg.) in 28 cc. 9:5 Me2CO-H2O shaken 22 hrs. over Pt from 100 mg. PtO2.H2O in 6 cc. H2O, and the crude product chromatographed on Al2O3 yielded 155 mg. 4-androstene-3,17-dione, m. 174-6°, [α]20D (c 0.505, absolute EtOH). The infrared absorption spectra of IV, VI, VII, IX, X, and XII are recorded.

L6 ANSWER 14 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1962:442508 CAPLUS
DOCUMENT NUMBER: 57:42508
ORIGINAL REFERENCE NO.: 57:8425d-i
TITLE: Chemistry of permaleic acid
AUTHOR(S): White, R. W.; Emmons, W. D.
CORPORATE SOURCE: Rohm & Haas Co., Philadelphia, PA
SOURCE: Tetrahedron (1962), 17, 31-4
CODEN: TETRAB; ISSN: 0040-4020
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

AB cf. CA 50, 3998d. The usual safety precautions (Greenspan, CA 41, 5445d) regarding the use of highly concentrated H2O2 were rigorously observed. Ice-cold CH2Cl2 (150 ml.) containing 11.6 g. 90% H2O2 stirred with instantaneous addition of 39.2 g. freshly crushed maleic anhydride (I), the solution refluxed with addition of 20 g. Me2CHCH2 COMe in an equal volume of CH2CI2, the disappearance of permaleic acid (II) followed by iodimetric titration of aliquots, the cooled II-free mixture filtered from precipitated maleic acid (III), the filtrate washed twice with 100 ml. 10% aqueous Na2CO3, once with 100 ml. 10% aqueous NaHSO3, and once with 100 ml. saturated aqueous NaCl, the dried (MgSO4) solution evaporated, and the residue distilled yielded 72% Me2CHCH2OAc, b. 115-16° n25D 1.3908. CH2Cl2 (70 ml.) containing 3.4 g. 90% H2O2, and 12.3 g. I similarly refluxed with addition of 6.6 g. 2,4,6-Br3C6H2NH2, the mixture refluxed 1 hr., the product isolated as above, and the solvent evaporated gave 6.5 g. 2,4,6-Br3C6H2NO2, m. 122-4°. A peracid solution at 0° prepared from 0.3 mole 90% H2O2, 0.38 mole I, and 150 ml. CH2C2 treated with 0.2 mole C6H13CH:CH2 in an equal volume of CH2Cl2, the mixture kept 1.8 hrs., and the II-free mixture worked up yielded 80% I-octene oxide, b10 51-4°, n25D 1.4150. CH2Cl2 (10 ml.) containing 40 ml. 90% H2O2 and 50 ml. I refluxed with addition of 10 ml. **estrone** acetate in 5 ml. CH2Cl2, the refluxing continued 16 hrs., the precipitated III filtered off, the washed and dried filtrate evaporated, the reddish solid chromatographed on 35 g. cationic Al2O3 (Woelm, activity I), eluted with C6H6 to give 1 g. starting material, and eluted with 600 ml. Et2O gave 40% estrono-lactone acetate, m. 142-4°. Further elution with 500 ml. MeOH gave 1.0 g. **amorphous** quinoid-type material possibly arising for attack of II on the A ring. II oxidized all classes of ketones smoothly and easily to the corresponding esters with no noticeable transesterification of products. Unsubstituted and neg. substituted anilines quickly and easily yielded the corresponding nitro compds. in high yield, whereas anilines with strongly electron donating groups were overoxidized to phenolic products. Internal olefins such as 9-nonadecene or 1-methylcyclohexene reacted rapidly with II at 0° but only products derived from an acid-catalyzed attack on the intermediate epoxide were isolated. Epoxidn. of deactivated double bonds was possible as in

epoxidn, of 1-octene at 0° to yield 80% 1-octene oxide and of H2C:CMeCO2Me, H2C: CHCO2Et, and (H2C:CHCH2)2SO to give Me α-methylglycidate, b16 50°, Et glyeidate, b17 60-2°, and (H2C:CHCH2)2SO2, b0.4 88-90°, in 74, 33, and 87% yields resp.

L6 ANSWER 15 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1962:60746 CAPLUS
DOCUMENT NUMBER: 56:60746
ORIGINAL REFERENCE NO.: 56:11657f-i
TITLE: A synthesis of D-norsteroids
AUTHOR(S): Cava, M. P.; Moroz, E.
CORPORATE SOURCE: Ohio State Univ., Columbus
SOURCE: Journal of the American Chemical Society (1962), 84, 115-16
CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
OTHER SOURCE(S): CASREACT 56:60746
AB A procedure is described for the conversion of 17-oxosteroids to novel norsteroids containing a 4-membered D-ring. 16-Oximinoestrone Me ether (prepared by the basecatalyzed nitrosation of **estrone** Me ether) with chloramine in aqueous tetrahydrofuran yielded 81% 16-diazoestrone Me ether, m. 145-6°, which irradiated with ultraviolet light in aqueous tetrahydrofuran containing NaHCO3 and then acidified gave 63%. I (X = β-CO2H) (II), m. 188-9°. II with CH2N2 gave the Me ester, m. 103-4°. II reduced with LiAlH4 gave 78% I (X = CH2OH), m. 141-2°, which with MeSO2Cl yielded 72% I (X = CH2OSO2Me) (III), m. 154-5°. III with PhSNa in warm Me2SO gave 75% I (X = PhSCH2), m. 111-12°, which desulfurized with Raney Ni in EtOH yielded 68% I (X = Me), m. 50-1°. Lumiestrone Me ether (IV) nitrosated with BuONO and Me3COK yielded 91% 16-oximino derivative of IV, m. 147-8% which with chloramine gave 82% 16-diazo derivative (V) of IV, m. 143-5°. V irradiated with ultraviolet light yielded an **amorphous** acid, m. 63-4°, which contained none of the crystalline II.

L6 ANSWER 16 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1962:60741 CAPLUS
DOCUMENT NUMBER: 56:60741
ORIGINAL REFERENCE NO.: 56:11647h-i,11648a-i,11649a-e
TITLE: Dehydrogenation of steroids. IV. Dienol-benzene re arrangement
AUTHOR(S): Dannenberg, Heinz; Hans-Guenter, Neumann
CORPORATE SOURCE: Max-Planck-Inst. Biochem., Munich, Germany
SOURCE: Ann (1961), 646, 148-70
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
OTHER SOURCE(S): CASREACT 56:60741
GI For diagram(s), see printed CA Issue.
AB cf. CA 55, 10504i. The dienol-benzene rearrangement proceeded by 1,4-dien-3-one steroids (I and 1,4,6-trien-3-one steroids (II) after direct or homologous reduction of the oxo group, analogously to the acid-catalyzed dienone-phenol rearrangement in the presence of Ac2OH2SO4. Thus, I and II yielded 4-methyl and 1-methyl ring A-benzoid compds. The dienol-benzene and the dienonephenol rearrangements were of the same type. The proof for the 4-position of the Me group in 4-methyl-19-nor-1,3,5(10)-cholestatriene (III), obtained by reduction of 1,4-cholestadien-3-one (IV) with LiAlH4 and subsequent treatment with acid, was given by the dehydrogenation with Se to 3',8-dimethyl-1,2-cyclopentenophenanthrene (V). IV (5.0 g.) in 100 cc. Et2O added with stirring during 0.5 hr. to 1.0 g. LiAlH4 in 100 cc. dry Et2O, the mixture diluted with 25 cc. Et2O, refluxed 0.5

hr., worked up, the resulting 4.9 g. mixture of oil and crystals dissolved in 125 cc. 96% EtOH, refluxed 0.5 hr. with 5 cc. concentrated HCl, poured into 300 cc. H2O, extracted with Et2O, and the oily residue from the extract (4.4 g.) chromatographed on Al2O3 gave 3.7 g. III, m. 49°. The crude product from a similar run with 3.5 g. IV dissolved in petr. ether and filtered gave 350 mg. crystalline C54H86O (VI), m. 216-18° (C6H6-Me2CO). VI (121 mg.), 20 cc. EtOH, and 1 cc. concentrated HCl refluxed 0.5 hr. and the product chromatographed on Al2O3 yielded 90 mg. III. IV (1 g.) in 20 cc. dry Et2O added dropwise at room temperature to MeMgI from 200 mg. Mg and 1.1 g. MeI in Et2O, the mixture stirred 1 hr., worked up, and 375 mg. of the crude product (1.07 g.) heated 0.5 hr. on the water bath with 0.3N HCl gave 150 mg. oily 1-Me derivative of III, [α]22D 155.5°. 1,4-Androstadiene-3,17-dione (200 mg.) in 15 cc. EtOH added dropwise to 50 g. fructose in 500 cc. H2O and 25 g. bakers' yeast, the mixture fermented 3 days at about 20°, extracted with Et2O, and the extract worked up gave 168 mg. 1,4-androstadien-17β-ol-3-one (VII), m. 168° (aqueous MeOH). VII (150 mg.) in 15 cc. dry Et2O added at room temperature dropwise to 20 equivs. MeMgI in Et2O, the mixture poured onto ice and aqueous NaHCO3, extracted with Et2O, the residual oil (160 mg.), containing about 50% 3-methylene-1,4-androstadien-17β-ol, refluxed 0.5 hr. with 20 cc. EtOH and 1 cc. concentrated HCl, and the crude product (150 mg.) chromatographed on Al2O3 gave 1,4-dimethyl-1,3,5(10)-estratrien-7β-ol-MeOH (VIII.MeOH), m. 74° (MeOH); VIII m. 64°, [α]23D 153.7° (EtOH). VIII (58 mg.), 4 cc. C5H5N, and 2 cc. Ac2O heated 1 hr. on the water bath gave the oily acetate, [α]27D 110° (EtOH), Rf 0.79 (C6H6). VIII (35 mg.) in 2 cc. C5H5N and 200 mg. 3,5(O2N)2C6H3COCl heated 0.5 hr. on the water bath yielded 38 mg. 3,5-dinitrobenzoate of VIII, m. 208° (CHCl3-MeOH), m. 208°. 1,4-Androstadiene-3,17-dione (1 g.) in dry Et2O added dropwise at room temperature to MeMgI from 500 mg. Mg and 2.84 g. MeI in Et2O, the mixture heated 1 hr., and worked up gave 180 mg. solid, which recrystd. twice from cyclohexane yielded 10 mg. 3,17-dimethyl-1,4-androstadiene-3ξ,17βdiol, m. 188°; the mother liquor evaporated and heated in PrOH or treated with alc. HCl or HCO2H at 20 and at 100° gave mixts. of various substances. Testosterone propionate (IX) (5.167 g.) in 160 cc. dry Et2O treated at -2° with a few drops HBr-AcOH and then 4.875 g. Br in 45 cc. AcOH, evaporated after 10 min., filtered, the filtrate evaporated in vacuo, and the residues combined gave 5.86 g. 2,6-Br2 derivative (X) of IX, m. 159-60° (decomposition) (CHCl3-EtOH); it decomposed soon in air with browning. X (5.8 g.) and 30 cc. collidine refluxed 0.5 hr., cooled, filtered, the filtrate poured with cooling into 6N HCl, extracted with Et2O, and the residue from the extract chromatographed on Al2O3 yielded 2.15 g. 1,4,6-androstatrien-17β-ol-3-one propionate (XI), m. 130-2° (Me2CO-hexane), [α]23D -9.4° (EtOH). XI (600 mg.) and excess (iso-PrO)3Al in 40 cc. absolute iso-PrOH refluxed 6 hrs. with overhead removal of distillate, added dropwise to 7 cc. concentrated HCl and 40 cc. iso-PrOH, refluxed 0.5 hr., diluted with H2O, extracted with Et2O, the residue from the extract heated 1 hr. on the water bath with 6 cc. C5H5N and 3 cc. Ac2O, and the crude product chromatographed on Al2O3 yielded 335 mg. acetate (XII) of 1-methyl-1,3,5(10),6-estratetraen-17β-ol (XIII), leaflets, m. 115° (MeOH), [α]25D -142° (EtOH). XII (150 mg.) in 0.5N KOH-MeOH refluxed 1 hr., diluted with H2O, extracted with Et2O, and the crude product chromatographed twice on Al2O3 yielded 50 mg. oily XIII, [α]25D -89° (EtOH). XII (250 mg.) in MeOH hydrogenated 45 min. with 100 mg. prehydrogenated PdO, filtered, evaporated, and the residue

chromatographed on Al2O3 yielded 200 mg. acetate (XIV) of 1-methyl-1,3,5(10)-estratrien-17β-ol (XV), m. 125° (MeOH), [α]25D 134° (EtOH), Rf 0.66 (C6H6). XIV (70 mg.) and 15 cc. 0.5N KOH-MeOH refluxed 35 min. under N, diluted with H2O, and extracted with Et2O yielded 10 mg. XV, m. 103° (MeOH), [α]25D 144° (EtOH), Rf 0.49 (95:5 C6H6-Me2CO). XI (2.15 g.) in 100 cc. dry Et2O added dropwise with stirring during 0.5 hr. to 2 g. LiAlH4 in 100 cc. dry Et2O, refluxed 0.5 hr., worked up, the crude product refluxed 0.5 hr. with 50 cc. EtOH and 2 cc. concentrated HCl, diluted with H2O, extracted with Et2O, the residue from the extract (2 g.) kept 13 hrs. in 20 cc. C5H5N and 10 cc. Ac2O, and the crude product chromatographed 4 times on Al2O3 yielded 25 mg. pure XII, and 30-40% 4,6-androstadien-17β-ol-3-one acetate, needles, m. 142° [α]24D -9.8° (EtOH). Crude 1,4,6-cholestatrien-3-one (4.4 g.) reduced with 1 g. LiAlH4 in Et2O, the crude product (4 g.) treated with 1.5 cc. concentrated HCl in 150 cc. EtOH, and chromatographed on Al2O3 gave 120 mg. oily material, which subjected to a 23-transfer countercurrent distribution gave oily 1-methyl-19-nor-1,3,5(10),6-cholestatetraene. XI (250 mg.) in 20 co. dry Et2O treated dropwise with 20 equivs. McMgI in Et2O, the resulting 215 mg. light yellow oil refluxed 1 hr. with 50 cc. EtOH and 2.4 cc. concentrated HCl, diluted with H2O, extracted with Et2O, and the crude product (190 mg.) chromatographed on Al2O3 gave 75 mg. 3-Me derivative containing some 4,6-dien-3-one; the mixture (75 mg.), 3 cc. C5H5N, and 1.5 cc. Ac2O heated 1 hr. on the steam bath, and the crude product (79 mg.) chromatographed on Al2O3 gave 50 mg. 3-Me derivative (XVI), needles, m. 142° (MeOH), [α]25D -148.5° (EtOH). XVI (30 mg.) in MeOH hydrogenated over 40 mg. prehydrogenated PdO gave the 3-Me derivative (XVII) of XIV, m. 103° (MeOH), [α]26D 137° (EtOH). Crude XVII (76 mg.) refluxed 1 hr. with 10 cc. 0.5N KOH-MeOH, diluted with H2O, extracted with Et2O, and the residue from the extract chromatographed on Al2O3 yielded 55 mg. impure 1-Me derivative of XV, which treated with 3,5-(O2N)2C6H3COCl and chromatographed gave 11 mg. 3,5-dinitrobenzoate, m. 224° (CHCl3MeOH). III (5 g.) and 6.5 g. **amorphous** Se heated 2 hrs. at 280-300° and 10 hrs. at 340-60°, cooled, boiled with C6H6, and chromatographed twice on Al2O3 yielded 35 mg. V, m. 110-20°, and 21 mg. XVIII, leaflets, m. 249.5-50.5°. III (4.36 g.) and 6 g. Se heated during 12 hrs. to 325° and the crude product chromatographed repeatedly on Al2O3 gave 7.5 mg. 8-methyl-3'-isooctyl- or 3',8-dimethyl-3'-isooctyl-1,2-cyclopentenophenanthrene (XIX), m. 94.5°, 98.5 (on Kofler block), 27.8 mg. hydrocarbon, m. 81°, which gave with 1,3,5-C6H3(NO2), an adduct, m. 132-3° (EtOH), and traces of V. Crude XIX (850 mg.) again heated 12 hrs. with 700 mg. Se at 335° and chromatographed on Al2O3 gave 10.5 mg. V, needles, m. 129-30° (EtOH).

L6 ANSWER 17 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER:	1961:56329 CAPLUS
DOCUMENT NUMBER:	55:56329
ORIGINAL REFERENCE NO.:	55:10811g-i,10812a-d
TITLE:	Long-acting steroid compounds
PATENT ASSIGNEE(S):	Charles E. Frosst & Co.
DOCUMENT TYPE:	Patent
LANGUAGE:	Unavailable
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 855716		19601207	GB 1958-29669	19580916

QAZI

US 3032469 19620501 US 1958-732490 19580502

AB In Brit. 738,230 (CA 50, 10814i), the preparation of hydrazones of keto steroids is described. Certain steroid hydrazones have been found to possess long-acting hormonal activity. Steroid esters react with aliphatic monocarboxylic acid hydrazides to form the corresponding steroid ester hydrazones. 3-Hydrazones of the 17-esters of testosterone enanthate (I), propionate (II), benzoate (III), and cyclohexylpropionate (IV) are prepared by treating 5 g. I with 3.1 g. of benzilic acid hydrazide, refluxing for 2 hrs. in 150 ml. of MeOH and a trace of glacial AcOH. The solvent is removed by distillation and the residue is crystallized to give 3-benzilic acid hydrazone of I, m. 108-10° (di-iso-Pr ether-di-Et ether), (α)D +156° (EtOH). Similarly prepared are: 3-mandelic acid hydrazone of I, m. 165-8° (di-Et ether-MeOH), (α)D +113 (EtOH); 3-diphenylacetic acid hydrazone of I, m. 209-11° (crystallized directly from solution), (α)D + 181.9° (CHCl3); 3-benzilic acid hydrazone of II, m. 132-5° (di-iso-Pr ether-di-Et ether), (α)D +141.5° (EtOH); 3-phenylacetic acid hydrazone of II, m. 130-3° (MeOH-di-iso-Pr ether), (α)D +141.5° (EtOH); 3-diphenylacetic acid hydrazone of II, m. 242-7° (MeOH), (α)D +186.9° (CHCl3); 3-benzilic acid hydrazone of III, m. 146-8° (di-Et ether-n-hexane), (α)D +215.8° (EtOH); 3-phenylacetic acid hydrazone of III, m. 115-19° (on evaporation of the solution, the product is obtained as an **amorphous** solid), (α)D +221.9° (CHCl3); 3-diphenylacetic acid hydrazone of III, m. 138-44° (**amorphous** solid), (α)D +208.9° (CHCl3); 3-mandelic acid hydrazone of IV, m. 179-81° (etherhexane), (α)D +150.8° (EtOH); 3-benzilic acid hydrazone of IV, m. 87-90° (**amorphous** solid), (α)D +141.1° (EtOH); 3-benzilic acid hydrazone of 19-nortestosterone 17-propionate, m. 103-7° (**amorphous** solid), (α)D +101° (EtOH).
In a similar manner, 17-hydrazones of the 3-esters of **estrone** enanthate (V), propionate (VI), benzoate (VII), and cyclohexylpropionate (VIII) were prepared Those prepared were: 17-phenylacetic acid hydrazone of V, m. 168-74° (MeOH), (α)D +45.6° (CHCl3); 17-mandelic acid hydrazone of VI, m. 85-103° (**amorphous** solid), (α)D +72° (EtOH); 17-diphenylacetic acid hydrazone of VI, m. 133-5° (benzene MeOH), (α)D +58.5 (CHCl3); 17-benzilic acid hydrazone of VII, m. 139-42° (EtOH), (α)D +85° (CHCl3); 17-mandelic acid hydrazone of VII, m. 137-43° (aqueous MeOH), (α)D +57.1° (CHCl3); 17-diphenylacetic acid hydrazone of VIII, m. 203-6° (MeOH), (α)D +48.6° (CHCl3); 17-benzilic acid hydrazone of VIII, m. 148-9° (di-iso-Pr etherdi-Et ether), (α)D +56.6° (CHCl3); 3-benzilic acid hydrazone of 17α-ethynyl-II, m. 149-52° (di-iso-Pr etherdi-Et ether), (α)D +94.3° (EtOH); 3-benzilic acid hydrazone of 17α-hydroxyprogesterone 17-enanthate, m. 89-101° (aqueous MeOH), (α)D +112.3 (CHCl3). These steroid ester hydrazones were studied in castrated and ovariectomized rats and showed far greater and prolonged biol. activity than did the non-hydrazone-esterified parent compds.

L6 ANSWER 18 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1959:83600 CAPLUS
DOCUMENT NUMBER: 53:83600
ORIGINAL REFERENCE NO.: 53:15121d-f
TITLE: D-Glucopyranosiduronates. II. Infrared absorption spectra of some methyl (steroidyl-2,3,4-tri-O-acetyl-β-D-glucosid)uronates
AUTHOR(S): Smakula, Erika; Leftin, Jehaudah H.; Wotiz, Herbert H.
CORPORATE SOURCE: Boston Univ., Boston, MA

QAZI

SOURCE: Journal of the American Chemical Society (1959), 81, 1708-15
CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

AB Eleven steroid glucosiduronates were studied in the **amorphous** and crystalline states. These 2 methods gave complementary information in the difficult interpretation of the superficially simple yet complex spectra of these partially flexible mols. The spectra uniformly showed bands of proportionally high intensity which were due to the sugar moiety common to all compds. and chiefly arising from its 4 ester groups. The spectra were differentiated by a low-intensity proportion of bands arising from the functional groups of the parent steroids. Qual. intensity evaluation of these bands permitted an estimation of sugar ratio. The stretching vibrations of the glucosidic linkage were characteristically perturbed by the environmental influence of neighboring steroid bands.

L6 ANSWER 19 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1959:23490 CAPLUS
DOCUMENT NUMBER: 53:23490
ORIGINAL REFERENCE NO.: 53:4352d-g
TITLE: A-Ring hydroxyalkylated **estrone** and estradiol derivatives
INVENTOR(S): Hoehn, Willard M.; Johns, Wm. F.
PATENT ASSIGNEE(S): G.D. Searle and Co.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2853501		19580923	US 1957-699188	19571127

AB Aqueous 40% CH_2O (I) 10 is added to a solution of **estrone** Me ether (II) 15 in $(Cl_2CH)_2$ 240 parts, and anhydrous HCl rapidly bubbled through with vigorous agitation. After 2 hrs., addnl. I 10 parts is added followed after a total of 8 hrs. by 5 vols. of 1:1 saturated aqueous $NaHCO_3$-aqueous 10% caustic. The solution is extracted with $CHCl_3$, washed with H_2O, dried over anhydrous $MgSO_4$, and concentrated to dryness in vacuo. The **amorphous** residue, a mixture of x-chloromethyl-3-methoxyestra-1,3,5(10)-trien-17-ones, in a solution of fused NaOAc 50 in AcOH 270 parts is heated under reflux for 5 hrs., concentrated to 0.1 the original volume under reduced pressure, diluted with H_2O, and extracted with $CHCl_3$. On evaporation of the solvent, the residue, a mixture of MeOH 160, and K_2CO_3 30 in H_2O 50 parts is heated under reflux for 1 hr., cooled, diluted with H_2O, and extracted with $CHCl_3$. The extract is washed with H_2O, dried over anhydrous $MgSO_4$, and concentrated to dryness in vacuo. The residue crystallized from acetone yields 2-hydroxymethyl-3-methoxyestra-1,3,5(10)-trien-17-one (III), m. 163-4°. Chromatography of the acetone mother liquors on silica gel gives 4-hydroxymethyl-3-methoxyestra-1,3,5(10)-trien-17-one (IV), m. 200-2°. Similarly, **estrone** 3-acetate gives 3-hydroxy-2-hydroxymethylestra-1,3,5(10)-trien-17-one (V). II reduced in tetrahydrofuran with $LiAlH_4$ gives 2-hydroxymethyl-3-methoxyestra-1,3,5(10)-trien-17β-ol. Crystallization from acetone and recrystn. from EtOAc gives pure product, m. 198-200°. In a similar run IV with $LiAlH_4$ gives 4-hydroxymethyl-3-methoxyestra-1,3,5(10)-trien-17-ol (VII), m. 259-63° (2-ethoxyethanol). The reduction of 2-acetyl-3-methoxyestra-1,3,5(10)-trien-17-one with $NaBH_4$ to give

2-(α-hydroxyethyl)-3-methoxyestra-1,3,5(10)-trien-17-ol, m. 134-6°, is also described.

L6 ANSWER 20 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1958:104476 CAPLUS
DOCUMENT NUMBER: 52:104476
ORIGINAL REFERENCE NO.: 52:18527f-i,18528a-i,18529a-d
TITLE: Steroids. XCIV. Synthesis of 2-methyl and 1,2-dimethyl estrogens
AUTHOR(S): Iriarte, J.; Ringold, H. J.
CORPORATE SOURCE: Syntex S. A., Mexico City, Mex.
SOURCE: Tetrahedron (1958), 3, 28-36
CODEN: TETRAB; ISSN: 0040-4020
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
OTHER SOURCE(S): CASREACT 52:104476

AB cf. C.A. 52, 11107i. Several 2-Me and 1,2-di-Me substituted derivs. of **estrone** and estradiol were prepared from 2α-methyltestosterone (I) by way of the 1,4- and 1,4,6-unsatd. compds. I (2.2 g.) in 75 ml. tert-BuOH boiled 72 hrs. (N atmospheric) with 2.2 g. SeO2 and 2 ml. AcOH and the cooled suspension diluted with EtOAc, filtered through Celite and evaporated in vacuo, the residue treated with H2O and extracted with EtOAc, the extract washed successively with dilute aqueous Na2CO3, cold aqueous (NH4)2S, cold. aqueous NH4OH, dilute HCl, and H2O and the extract dried and evaporated, and the residue triturated with Et2O gave 1.5 g. material, m. 203-9°, supplemented by 0.25 g. material, m. 209-10°, obtained from chromatography of the mother liquors on neutral Al2O3 to give 80% 2-methyl-1,4-androstadien-17β-ol-3-one (II), m. 211-12° (Et2O), [α]D 6° (CHCl3), λ 248 mμ (log ε 4.23). II (3 g.) in 1.5 l. mineral oil passed through a Pyrex tube packed with glass beads at 600° and the cooled oil diluted with C6H14, the solution extracted with 5% NaOH and the alkaline extract acidified, the product chromatographed on 80 g. silica gel and eluted with 9:1 C6H6-Et2O, the fraction crystallized (Et2O-C6H14), and the product (0.5 g., m. 180-2°) recrystd. (Et2O) gave 2-methylestradiol (III), m. 185-6°, [α]D 78° (dioxane), λ 284 mμ (log ε 3.38); 3-monobenzoate (IIIa), m. 187-90° (Et2O), λ 226, 270 mμ (log ε 4.37, 3.58). IIIa (0.125 g.) in 5 ml. AcOH treated with 0.25 g. CrO3 in 2.5 ml. AcOH and the solution kept at 25° 1 hr., diluted with H2O, and filtered gave 0.08 g. 2-methylestrone benzoate, m. 212°, [α]D 183° (dioxane), λ 226, 270 mμ (log ε 4.36, 3.54), converted by boiling 0.1 g. with 5 ml. 1% KOH in MeOH 1 hr. and neutralizing with AcOH, treating the concentrated solution with brine and extracting with Et2O, decolorizing (C), and recrystg. (Et2O) to give 0.05 g. pure 2-methylestrone (IV), m. 221-5° [α]D 198° (dioxane), λ 283 mμ (log ε 3.41). AcOH (40 ml.) containing 3 g. 2α-methyl-17β-androstanol-3-one (cf. R. and Rosenkranz, C.A. 51, 17974c) treated in 10 min. with 1.5 g. CrO3 in 10 ml. H2O and 40 ml. AcOH and the mixture kept 1 hr. at 25°, poured into H2O and the crystalline precipitate washed and dried, crystallized (Et2O-C6H14), and the product (2.3 g., m. 148.9°) recrystd. gave 2α-methylandrostane-3,17-dione (V), m. 152-3°, [α]D 110° (CHCl3). V (1.0 g.) in 30 ml. AcOH treated slowly at 18° with 15.2 ml. Br in AcOH 0.07 g./ml.) and the solution kept 1 hr., poured into 300 ml. ice H2O and the washed and dried product [1.25 g., m. 140-5° (decomposition)] boiled 4

hrs. (H2O-free atmospheric) in 20 ml. γ-collidine, the cooled mixture diluted with Et2O and filtered from 0.87 g. amine HBr salt, the residue washed with Et2O and the combined filtrate and washings washed with excess 5% HCl, H2O, and aqueous NaHCO3, the dried solution evaporated and the residue chromatographed on 20 g. neutral Al2O3, eluted with 2:1 C6H6-Et2O, and the fraction (0.56 g., m. 183-8°) recrystd. (Et2O) yielded 2-methyl-1,4-androstadiene-3,17-dione (VI), m. 198-200°, [α]D 100° (CHCl3), λ 247 mμ (log ε 4.20). Similar CrO3-AcOH oxidation of 1 g. II gave 0.8 g. VI. I (10 g.) in 100 ml. AcOH treated in 10 min. with 5 g. CrO3 in 25 ml. H2O and 150 ml. AcOH and the mixture kept 1 hr. at room temperature, poured into H2O, and the dried H2O-washed precipitate (8.6 g., m. 155-9°) crystallized (Et2O) gave 2α-methyl-4-androstene-3,17-dione (VII), m. 159-60°, [α]D 190° (CHCl3), λ 242 mμ (log ε 4.22). VII (10 g.) in 500 ml. anhydrous Et2O at 0° stirred (H2O-free atmospheric) with dropwise addition of 12 g. Br in 20 ml. AcOH and the mixture treated at room temperature with 200 ml. H2O, the Et2O evaporated in vacuo at 25°, the mixture filtered, and the precipitate washed with H2O and 5 ml. cold MeOH yielded 10.6 g. crude 2,6-dibromo compound (VIII), m. 115-20° (decomposition), recrystd. (MeOH) to give 2,6-dibromo-2-methyl-4-androstene-3,17-dione, m. 128-32° (decomposition), [α]D 49° (CHCl3), λ 251 mμ (log ε 4.11). VIII (6 g.) in 25 ml. γ-collidine refluxed 1 hr. (H2O-free atmospheric) and the cooled solution diluted with EtOAc, filtered and the precipitate (4.8 g.) washed with EtOAc, the filtrate and washings washed with dilute HCl and H2O and the residue (3.5 g.) chromatographed on 150 g. neutral Al2O3, eluted with C6H6-Et2O, and the fraction recrystd. (EtOAc-Et2O) gave 2.1 g. 2-methyl-1,4,6-androstatriene-3,17-dione (IX), m. 197.5-99°, [α]D 60° (CHCl3), λ 266, 301 mμ (log ε 4.04, 3.98). VIII (1.1 g.) refluxed 20 min. in 7 ml. 1:1 γ-collidine-xylene and the cooled solution diluted with EtOAc, filtered and the filtrate washed with dilute HCl and H2O, the dried solution evaporated in vacuo, and the residue crystallized (MeOH) gave 0.28 g. material, m. 211-13° (decomposition), recrystd. (MeOH) to give 6-bromo-2-methyl-1,4-androstadiene-3,17-dione, m. 216-18°, [α]D 32° (CHCl3), λ 246 mμ (log ε 4.20). IX (5 g.) heated 5 hrs. at 90° in 100 ml. Ac2O with 2 g. p-MeC6H4SO3H.H2O and the cooled solution poured into ice H2O with stirring, filtered and the precipitate washed thoroughly with H2O and air-dried, crystallized (MeOH), and the product (4.34 g., m. 178-80°) recrystd. (MeOH) gave 1,2-dimethyl-6,7-dehydroestrone acetate (X), m. 180-1°, [α]D -53° (dioxane), λ 225, 266 mμ (log ε 4.45, 3.11). X (1.7 g.) boiled 30 min. (N atmospheric) in 400 ml. 1% KOH in MeOH and 10 ml. AcOH added, the mixture concentrated to 30 ml. and diluted with brine, filtered, and the precipitate recrystd. (EtOAc and MeOH) yielded 74% pure 1,2-dimethyl-6,7-dehydroestrone (Xa), m. 254-5°, [α]D -44° (dioxane), λ 231, 272, 306 mμ (log ε 4.45, 3.92, 3.38). X (1.13 g.) in 50 ml. EtOAc hydrogenated 1 hr. at 25°/570 mm. with 50 mg. prereduced 10% Pd-C and the filtered solution evaporated gave 1.1 g. product, m. 204-6°, crystallized (MeOH) to give 1,2-dimethylestrone acetate (XI), m. 210-11°, [α]D 223° (dioxane), λ 272, 280 mμ (log ε 2.73, 2.73). Hydrolysis of 0.5 g. XI as described for X gave 0.41 g. material, m. 267-75°, recrystd. (MeOH) to give 1,2-dimethylestrone (XIa), m. 274-5°, [α]D 257°

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(CHCl3), 270° (dioxane), λ 288 mμ (log ε 3.36). X (0.52 g.) in 100 ml. MeOH boiled 10 min. with 0.7 g. NaBH4 in 2 ml. H2O and the solution kept 1 hr. at room temperature, treated with 5 ml. AcOH and concentrated in vacuo, the cooled solution poured into ice H2O and the mixture extracted with EtOAc, the extract evaporated, and the product (0.43 g., m. 229-31°) recrystd. (MeOH) gave 1,2-dimethyl-6,7-dehydroestradiol (XII), m. 231-2°, [α]D -110° λ 230, 270-2, 306-8 mμ (log ε 4.49, 3.99, 3.41). Ia (0.22 g.) in 100 ml. MeOH kept 16 hrs. at room temperature with 0.25 g. NaBH4 in a few ml. H2O, treated with 2 ml. AcOH and the solution concentrated in vacuo, the gummy residue taken up in H2O and the solution extracted with EtOAc, the extract evaporated, and the residue triturated with C6H14 gave **amorphous** 1,2-dimethylestradiol (XIII), m. 120-5°, [α]D 149° (dioxane), λ 288 mμ (log ε 3.25). Optical data for substituted estrones and estradiols were tabulated [compound, [α]D (dioxane), [M]D, [M]D (1-Me, 2-Me), and λ mμ (alc.) (log ε) given]. Estrones: **estrone**, 163°, 460, -, -, 280 (3.37); 1-methylestrone, 247°, 731, 271, -, 287 (3.23); IV, 198°, 586, -, 126, 283 (3.41); XIa, 258, 800, -, 69, 288 (3.36); 6,7-dehydroestrone, -124°, -347, -, -, 221, 262, 306 (4.49, 3.95, 3.40); 1-methyl-6,7-dehydroestrone, -77°, -226, 121, -, 228, 267, 276, 304 (4.49, 3.92, 3.82, 3.29); Xa, -44°, -136, -, 90, 231, 272, 306 (4.45, 3.94, 3.38). Estradiols: estradiol, 80°, 227, -, -, 280 (3.33); 1-methylestradiol, 146°, 435, 208, -, 284 (3.28); III, 78°, 232, -, 5, 284 (3.38); XIII, 149°, 465, -, 30, 288 (3.25); 6,7-dehydroestradiol, -169°, -477, -, -, 222, 263, 306 (4.50, 3.98, 3.52); 1-methyl-6,7-dehydroestradiol, -126°, -373, 104, -, 305 (3.20); XII, -110°, -328, -, 40, 230, 271, 307 (4.49, 3.99, 3.41). Although the contribution of a planar 2-Me group is insignificant the 1-Me estrogens exhibit a pos. mol. rotation increment varying from 104 to 271, due probably to interaction between the C-1 Me and the C-11 methylene group (cf. Djerassi, et al., C.A. 51, 5110a). The ultraviolet bathochromic shift attributable to the C-2 Me group is very slight and that due to a C-1 Me group only slightly greater. An individual C-1 or C-2 Me group decreases estrogenic activity by a factor up to 200. The activity decrease for 2 Me groups is not completely cumulative but XIa and Xa exhibit less than 1/2000 the uterotropic activity of **estrone** in the mouse assay. Both are potent antiandrogens as determined by their antagonism to testosterone in the chick comb. assay.

L6 ANSWER 21 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER:	1958:98124 CAPLUS
DOCUMENT NUMBER:	52:98124
ORIGINAL REFERENCE NO.:	52:17326a-i,17327a-h
TITLE:	Preparation and reactions of 11-substituted 1,3,5(10)-estratrienes. I. 11-Oxygenated estrones and estradiols
AUTHOR(S):	Magerlein, Barney J.; Hogg, John A.
CORPORATE SOURCE:	Upjohn Co., Kalamazoo, MI
SOURCE:	Journal of the American Chemical Society (1958), 80, 2220-5 CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE:	Journal
LANGUAGE:	Unavailable
OTHER SOURCE(S):	CASREACT 52:98124

QAZI

AB cf. C.A. 51, 11367c. 11α-Hydroxyprogesterone (50 g.) in 550 cc. Me3COH treated at 55° with 82.5 cc. (CO2Et)2 and 82.5 g. 25% NaOMe in MeOH, then with 18.6 g. NaOAc and 21.9 cc. AcOH in 590 cc. MeOH, cooled to 0°, 76 g. Br in 400 cc. MeOH added during 15 min. with cooling, and, without cooling, 155 g. 25% NaOMe-MeOH, and the mixture stirred 1.5 hrs. at room temperature, poured with stirring into 4 vols. iced H2O, and filtered gave a crude **amorphous** product; a 20-g. portion in 60 cc. collidine refluxed 50 min., poured into cold dilute HCl, filtered, and the residue air-dried gave 14.5 g. crude Me 11α-hydroxy-3-oxo-1,4,17(20)-cis-pregnatrien-21-oate (I); a 10-g. portion of the crude I chromatographed on 200 g. Florisil and recrystd. (EtOAc) yielded 1.07 g. pure I, m. 245-52°, [α]D 141° (Me2CO) (all m.ps. are corrected). I with Ac2O and C5H5N gave the acetate, m. 140-2° (EtOAc-Skellysolve B). Progesterone was converted similarly to 40% Me 3-oxo-1,4,17-(20)-cis-pregnatrien-21-oate (II), m. 173-7°. II (3.0 g.) in 300 cc. mineral oil passed at the rate of 10 cc./min. through a Vycor glass tube packed with Pyrex helices at 550°, the liquid pyrolysis product kept 3-4 days at 2°, the oil decanted from the precipitate, and the residue dissolved in 160 cc. CH2Cl2 and chromatographed over 80 g. Florisil gave 539 mg. solid; the decantate diluted with 3 vols. Skellysolve B and chromatographed on 160 g. Florisil yielded 413 mg. crystalline material; the combined solids recrystd. (MeOH) yielded 440 mg. Me 3-hydroxy-19-nor-1,3,5(10),17-(20)-pregnatetraen-21-oate (III), m. 138.5-41°; there was evidence for a polymorphic form, m. about 165°. III (440 mg.) in 1.5 cc. Ac2O and 3.0 cc. C5H5N kept 18 hrs. at 26°, poured into iced H2O, and filtered gave 410 mg. acetate (IV) of III, m. 165-7° (EtOAc). IV (100 mg.) in 30 cc. CH2Cl2 treated at -78° with 0.31 millimole O3, the solvent distilled at 20 mm., the residue dissolved in 15 cc. AcOH, the solution stirred 1.5 hrs. with 150 mg. powdered Zn, filtered, concentrated in vacuo to 2-3 cc., diluted with CH2Cl2, washed with dilute HCl, dried, evaporated, and the residue chromatographed on Florisil yielded 19 mg. **estrone** acetate, m. 122-5° (MeOH). I (5.5 g.) pyrolyzed at 600° in 500 cc. 1,2,3,4-tetrahydronaphthalene and 50 cc. mineral oil, and the effluent chromatographed on 200 g. Florisil yielded 2.65 g. 11α-HO derivative (V) of III, oil. Crude V (3.1 g.) acylated in the usual fashion and chromatographed on 200 g. Florisil gave 3.2 g. oily diacetate (VI) of V. VI (3.2 g.) in 200 cc. CH2Cl2 ozonized in the usual manner and the crude product chromatographed on 250 g. Florisil gave 1.04 g. (crude) 3,11α-diacetoxy-1,3,5(10)-estratrien-17-one (VII), m. 172-3° (MeOH). VII (310 mg.) in 5 cc. C6H6 and 15 cc. Et2O refluxed 1 hr. with 0.5 g. LiAlH4 in 50 cc. Et2O yielded 213 mg. 3,11α,-17-trihydroxy-1,3,5(10)-estratriene (11α-hydroxyestradiol) (VIII), m. 250-1° (EtOAc). VIII (520 mg.) in 25 cc. MeOH and 5 cc. H2O containing 3 g. KOH treated at 5° with four 1.5-cc. portions of Me2SO4 at 0.5-hr. intervals, evaporated in an air stream, worked up in the usual manner, and the crude product chromatographed on 40 g. Florisil yielded 400 mg. 3-Me ether (IX) of VIII, m. 144-5° (Et2O). IX (400 mg.) in 35 cc. dry Et2O and 25 cc. liquid NH3 treated at -78° with 400 mg. Li, then during 0.5 hr. with 4 cc. EtOH, the NH3 evaporated, the residue diluted with H2O, processed, the crude oily product refluxed 0.5 hr. with 25 cc. MeOH containing 3 cc. H2O and 1 cc. concentrated HCl, extracted with CH2Cl2, and the extract chromatographed on 40 g. Florisil yielded 178 mg. 11α-hydroxy-19-nortestosterone, m. 179-81° (Me2CO). Crude 11α-acetoxy-3-oxo-17-carbomethoxymethylene-1,4-androstadiene (6 g.) ozonized in the usual manner with 10% excess O3, stirred 1 hr. at room temperature with 20 cc. AcOH and 1 g. powdered Zn while being treated with 4-5

further 1-g. portions of Zn dust, filtered, washed with dilute HCl, dried, and chromatographed on Florisil yielded 1.91 g. (crude) 11α-acetoxy-1,4-androstadiene-3,17-dione (X), m. 246-8° (EtOAc). X (1.5 g.) in 150 cc. heavy mineral oil pyrolyzed at 600°, the effluent diluted with Et2O, extracted with 5% aqueous NaOH, and the alkaline extract acidified and reextd. with Et2O yielded 710 mg. (crude) 3-hydroxy-1,3,5(10),9(11)-estratetraen-17-one (XI), m. 257-9° (EtOAc). XI (50 mg.) and 10 cc. glacial AcOH hydrogenated 0.5 hr. over 25 mg. PtO2, filtered, and evaporated yielded 20 mg. **estrone**, m. 228-33°. 11β-Hydroxy-1,4-pregnadiene-3,17-dione (1.0 g.) in 100 cc. C6H6, 40 cc. Et2O, 20 cc. H2O, and 40 cc. concentrated HCl refluxed 17 hrs. with stirring and the crude product chromatographed on Florisil yielded 1,4,9(11)-androstatriene-3,17-dione (XII), m. 164-6° (EtOAc), [α]D 102° (CHCl3). XII pyrolyzed in the usual manner yielded 29% XI, m. 255-7°. XI (50 mg.) in 1.5 cc. MeOH and 0.6 cc. H2O containing 0.5 g. KOH treated with 0.6 cc. Me2SO4, the MeOH evaporated, the residue diluted with H2O, extracted with CH2Cl2, and the extract worked up gave 35 mg. Me ether (XIII) of XI, m. 142-5° (Et2O-Skellysolve B). XIII (35 mg.) in 15 cc. Et2O, 1 cc. EtOH, and 25 cc. NH3 treated with 100 mg. Li, the NH3 evaporated, the residue extracted with CH2Cl2, the extract evaporated, the residue refluxed 0.5 hr. with 15 cc. MeOH, 0.5 cc. HCl, and 2 cc. H2O, and the mixture worked up yielded 9 mg. 19-nortestosterone (XIIIa). The 11β-HO analog of X (1.69 g.) in 170 cc. heavy mineral oil pyrolyzed at about 600° at the rate of 10 cc./min., the eluent diluted with Et2O, extracted with 5% aqueous NaOH, the aqueous alkaline solution acidified, extracted with CH2Cl2, and the extract chromatographed on Florisil yielded 0.24 g. 3,11β-dihydroxy-1,3,5(10)-androstatrien-17-one (XIV), m. 254-7° (EtOAc), [α]D 194° (dioxane), and small amts. of XI. XIV with 1 mole equivalent of Ac2O and C5H5N yielded the monoacetate, m. 186-7°, [α]D 192° (CHCl3). XIV (150 mg.) and 160 mg. KOH in 1.6 cc. H2O and 8 cc. MeOH treated with 2.7 cc. Me2SO4, evaporated in vacuo, and the residue triturated with H2O gave 160 mg. Me ether (XV) of XIV, m. 169-70° (MeOH) with softening at 160°. XV (40 mg.) in 1 cc. EtOH, 10 cc. Et2O, and 25 cc. NH3 treated with 100 mg. Li, the NH3 evaporated, the residue extracted with CH2Cl2, the extract evaporated, the residue dissolved in 20 cc. MeOH, 2 cc. H2O, and 0.5 cc. HCl, and the solution neutralized after 15 min. at 26°, and chromatographed on Florisil gave 18 mg. 11β-HO derivative (XVI) of XIIIa. XV (160 mg.), 2 cc. 4M MeMgBr, and 25 cc. C6H6 refluxed 17 hrs., poured onto ice-HCl, and extracted with CH2Cl2 yielded 160 mg. (crude) 17-methyl-3-methoxy-1,3,5(10)-androstatriene-11β,17β-diol (XVII), m. 162-3° (EtOAc-Skellysolve B). XVII (380 mg.) in 10 cc. dioxane, 80 cc. NH3, and 2.5 cc. EtOH treated with 250 mg. Li, the mixture evaporated, the residue diluted with H2O, extracted with CHCl2, the crude residue from the extract refluxed 15 min. with 20 cc. MeOH containing 2 cc. H2O and 0.5 cc. concentrated HCl, treated with excess NaOAc, evaporated in vacuo, and the product isolated with CH2Cl2 yielded 140 mg. 17-methyl-11β,17β-dihydroxy-19-nor-4-pregnen-3-one, m. 219-24°, [α]D 67° (CHCl3). XV(3.1 g.) in 160 cc. C6H6 treated with a 20-fold excess of EtLi in hexane, kept 18 hrs. at 26°, diluted with iced H2O, the organic layer percolated through Florisil, and the effluent worked up gave 1.7 g. unchanged XV and 1.2 g. 17α-Et analog (XVIII) of XVII, m. 148-9° (iso-PrOH-Skellysolve B). XVIII (1.8 g.) in 40 cc. dioxane, 400 cc. NH3, and 15 cc. 95% EtOH treated in the usual manner with 1.5 g. Li and the crude product chromatographed on Florisil yielded 740 mg. 17α-Et derivative of XVI, m.

165-7° (Me2CO). Crude XIV (1.0 g.) reduced with LiAlH4 yielded 45% 11β-hydroxyestradiol, m. 291-5°. XIV (1.0 g.) acetylated with 5 cc. Ac2O and 7 cc. C5H5N, the resulting crude crystalline 3-methoxy-11β-acetoxy-1,3,5(10)-estratrien-17-one in 30 cc. dioxane, 10 cc. EtOH, and 150 cc. NH3 treated with 1 g. Li, the NH3 evaporated, and the product refluxed 15 min. with 50 cc. MeOH, 5 cc. H2O, and 1 cc. concentrated HCl, and chromatographed on Florisil yielded 85 mg. 17β-hydroxy-1-(2-hydroxyethyl)-4-estren-3-one (XIX), m. 221-2° (EtOAc). XIX (30 mg.) and 47 mg. CrO3 in 2 cc. AcOH containing 1 drop H2O kept 1 hr. at 5° and 2 hrs. at 25°, and the crude product chromatographed on Florisil yielded an oily product.

L6 ANSWER 22 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1958:61283 CAPLUS
DOCUMENT NUMBER: 52:61283
ORIGINAL REFERENCE NO.: 52:11103e-i,11104a-i,11105a-i,11106a-i,11107a-b
TITLE: Configuration of the estrones. Total synthesis of the remaining stereoisomers
AUTHOR(S): Johnson, William S.; David, Israel A.; Dehm, Henry C.; Highet, Robert J.; Warnhoff, E. W.; Wood, W. David; Jones, E. T.
CORPORATE SOURCE: Univ. of Wisconsin, Madison
SOURCE: Journal of the American Chemical Society (1958), 80, 661-79
CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
OTHER SOURCE(S): CASREACT 52:61283

AB Two addnl. stereoisomers of the **estrone** structure were synthesized. NaOH (120 g.), 600 cc. (CH2OH)2, and 60 cc. H2O heated to about 115°, the mixture treated with 11 g. 2-furfurylidene derivative (I) of trans-9-methyl-1-decahydronaphthalenone (II), m. 110.5-11°, refluxed 7.5 hrs., cooled, diluted with H2O, and steam distilled, the distillate (about 15 l.) extracted with Et2O, and the extract worked up gave 2.33 g. trans-9-methyl-1-decahydronaphthalenol (III), b9.5 about 114°, n25D 1.4990, and a 2nd fraction, 3.13 g., b1 about 144°, n25D 1.5220. Na2Cr2O7.2H2O (1.5 g.) in 7 cc. H2O, 2 cc. concentrated H2SO4, and 1.2 cc. glacial AcOH added slowly with stirring and cooling to 2.17 g. crude III in 10 cc. C6H6, stirred 2 hrs. at 0° and 2 hrs. at room temperature, washed, dried, and evaporated, and the residue treated with H2NCONHNH2.HCl and NaOAc in aqueous MeOH yielded 2.41 g. semicarbazone (IV) of II, m. 226-7° (decomposition). IV (3.74 g.) heated with aqueous (CO2H)2 and extracted with Et2O gave 2.38 g. II, b9.5 104-6°, n25D 1.4884, d25 0.9909, MRD 48.3. The cis isomer (V) of II, n25D 1.4894, d25 0.9918, MRD 48.3, was prepared by the method described previously (C.A. 37, 52922). The appropriate ketone (II or V) condensed with a suitable aromatic aldehyde by the method described previously (loc. cit.) but using MeOH yielded the corresponding arylmethylene derivs. of the ketones. In this manner were prepared the 2-(p-anisylidene) derivative (VI) of V, prisms, m. 110-11° (sublimed at 108°/0.02 mm.), and the 2-(p-anisylidene) derivative (VII) of II, plates, m. 110-11° (MeOH) [2,4-dinitrophenylhydrazone, yellow-orange prisms, m. 224-5° (CHCl3-EtOH)]. 1-Decahydronaphthalenone (VIII) (20 g.) and 18.2 g. p-MeOC6H4CHO in 500 cc. MeOH treated 3 days with 200 cc. 15% aqueous NaOH and 52 cc. H2O yielded 20.4 g. 2-(p-anisylidene) derivative (IX) of VIII and after 30 days an addnl. 12 g., m. 107-8° (MeOH) [2,4-dinitrophenylhydrazone, orange prisms, m. 223.5-24° and 245-6° (CHCl3-EtOH)]. IX methylated gave a mixture of 67% VI and 40% putative VII. In the same manner were prepared the 2-(p-chlorobenzylidene) derivative (X) of V, prisms, m. 112-12.7°

(MeOH) [2,4-dinitrophenylhydrazone, orange prisms, m. 184-5° (CHCl3-EtOH)], and the 2-(p-chlorobenzylidene) derivative (XI) of II, rods, m. 118.5-19.5° (MeOH and sublimed in vacuo) [2,4-dinitrophenylhydrazone, yellow rods, m. 236.5-7.5° (CHCl3-EtOH)]. VIII (38.3 g.) and 34.4 g. p-ClC6H4CHO gave in the usual manner 39.8 g. 2-(p-chlorobenzylidene) derivative (XII) of VIII, plates, m. 152.5-3.5° (MeOH) [2,4-dinitrophenylhydrazone, yellow needles, m. 217-18° (CHCl3MeOH)]. Methylation of XII gave a mixture containing 86% X and 16% XI.

V

condensed in the presence of NaOMe with p-Me2NC6H4CHO (XIII) and the product sublimed in vacuo and recrystd. from CHCl3-EtOH gave the 2-(p-dimethylaminobenzylidene) derivative (XIV) of V, pale yellow rods, m. 120-20.5°. In the same manner was obtained the trans isomer (XV) of XIV, pale yellow plates, m. 154-5° (CHCl3-EtOH), with a reflux period of 2 hrs. VIII (0.673 g.) and 0.722 g. XIII in 4.5 cc. 5% NaOMe in MeOH refluxed 45 min. gave 0.987 g. 2-(p-dimethylaminobenzylidene) derivative (XVI) of VIII, pale yellow plates, m. 169-70° (CHCl3-EtOH). Methylation of XVI gave 10% XVI, 49% XIV, and 29% XV. In the usual manner were prepared the 2-(p-nitrobenzylidene) derivative (XVII) of V, plates, m. 146-7° (CHCl3-EtOH) [2,4-dinitrophenylhydrazone, orange prisms, m. 197-8° (CHCl3-EtOH)], and the 2-(p-nitrobenzylidene) derivative (XVIII) of II, prisms, m. 181-2° (CHCl3-EtOH) [2,4-dinitrophenylhydrazone, yellow prisms, m. 223-4° (CHCl3-EtOH)]. VIII (15.0 g.) and 15.0 g. p-O2NC6H4CHO condensed during 30 hrs. in the usual manner yielded 20.2 g. 2-(p-nitrobenzylidene) derivative (XIX) of VIII, plates, m. 171-2° [2,4-dinitrophenylhydrazone, golden needles, m. 162-4° resolidifying and rem. 198-9° (CHCl3-EtOH)]. Methylation of XIX yielded 36% XIX, 39% XVII, and 20% XVIII. In the usual manner were prepared the 2-(1-naphthal) derivative (XX) of V, prisms, m. 120.5-21° (MeOH) [2,4-dinitrophenylhydrazone, orange needles, m. 211.5-12.5° (CHCl3-EtOH)], and the 2-(1-naphthal) derivative (XXI) of II, needles, m. 127-7.5° (MeOH) [2,4-dinitrophenylhydrazone, golden plates, m. 190-1° (CHCl3-EtOH)]. VIII (15.2 g.) and 15.6 g. 1-C10H7CHO gave in the usual manner during 2 days 17.3 g. 2-(α-naphthal) derivative (XXII) of VIII, plates, m. 107-8° (MeOH) [2,4-dinitrophenylhydrazone, yellow-orange prisms, m. 197.5-8.5° (CHCl3-MeOH)]. XXII methylated in the usual manner yielded 7% XXII, 62% XX, and 32% XXI. Crude mixed 5-hydroxy-5-[1-(p-anisylethyl)]-1-decahydronaphthalenone (from 99.2 g. m-MeOC6H4C.tplbond.CH and 124.5 g. decahydronaphthalene-1,5-dione) in 4 l. C6H6 treated with stirring at 0° with 310 g. AlCl3, stirred 1.5 hrs. at room temperature, and worked up, and the total crude product recrystd. from absolute EtOH containing a

little

C6H6 gave 43.5 g. dl-9-iso-18-nor-D-homoestrone Me ether (cis-anti-trans-methoxyhydrochrysenone) (XXIII), m. 166-70°; 2nd crop, 7.4 g., m. 167-70°. XXIII (0.881 g.) and 0.118 g. p-MeC6H4SO3H.H2O (XXIV) in 66.4 cc. Ac2O concentrated with distillation during

5 hrs.

to about 15 cc. and evaporated in vacuo, the residual dark oil dissolved in Et2O, the solution chilled, washed, dried, and evaporated, and the residue chromatographed on 10 g. Florex gave 0.891 g. 13,17a-enol acetate (XXV) of XXIII, platelets, m. 108-11° (methylcyclohexane). XXIII (0.096 g.) and 0.06 g. XXIV in 35 cc. AcOCMe:CH2 (XXVI) concentrated with distillation

during 10

hrs. to about 5 cc., the crude product retreated 10 hrs. in the same manner with XXVI and 0.65 g. XXIV, and the product chromatographed on 8 g. Florex yielded 0.066 g. 17,17a-enol acetate of XXIII, m. 122-3°, which was partially converted into the lower melting polymorph on drying at 80°/0.1 mm. 6 hrs. to give material, m. 120.5-25° with softening at 118°. XXIII (0.430 g.) and 0.83 g. SO2Cl2 in 25 cc.

CCl4 kept 12 hrs. at room temperature and evaporated in an air stream, and the residue dissolved in Et2O, washed, dried, and worked up gave oily chloroketone, C19H23ClO2; a 0.389-g. portion in 5 cc. collidine (XXVIII) refluxed 0.5 hr. under N, and the crude product chromatographed on 15 g. Al2O3, triturated with 95% EtOH, and recrystd. from 95% EtOH gave dl-13,14-dehydro derivative (XXVIII) of XXIII, m. 136-7.5° (chromatographed and recrystd. from C6H6-hexane) [2,4-dinitrophenylhydrazone, red blades, m. 194-4.4°, and red needles, m. 213.5-14.5° (CHCl3-EtOH), which were interchangeable polymorphic forms]; further elution of the original chromatogram gave 1-oxo-8-methoxy-1,2,3,4-tetrahydrophenanthrene, plates, m. 236-8° (hexane). Br (5.0 g.) in 400 cc. CCl4 added with stirring and cooling during 3.5 hrs. to 10.2 g. crude XXV in 450 cc. CCl4, the mixture treated with 20 g. NaHSO3 in 100 cc. H2O, the organic layer worked up, the red oily residue dissolved in 160 cc. HCONMe2, the solution heated 2 hrs. under N with 3.97 g. LiCl, most of the solvent distilled in vacuo, the residue dissolved in C6H6 and Et2O, the solution worked up, and the crude product chromatographed on 100 g. Florisil gave 4.2 g. XXVIII, m. 123-38.5°. Li (12 mg.) and 15 cc. liquid NH3 allowed to stand 5 min., treated with one half of a solution of 0.150 g. XXVIII in 6 cc. dry Et2O and 2 cc. dry dioxane, the mixture treated after 0.5 hr. with the other half of the solution and then with excess solid NH4Cl, the NH3 evaporated, the residue partitioned between Et2O and H2O, the organic layer worked up, and the pale amber, glassy residue chromatographed on 7.5 g. Al2O3 yielded 0.021 g. XXIII, needles, m. 167.5-9.5°. trans-anti-trans-Isomer (XXIX) of XXIII (0.132 g.), m. 154-6°, treated with 0.089 g. XXIV in 50 cc. Ac2O and the crude product chromatographed on 6.5 g. Florex gave 0.117 g. (crude) 13,17a-enol acetate (XXX) of XXIX, microprisms, m. 122-4° (methylcyclohexane). XXIX (0.132 g.), 40 cc. XXVI, and 0.89 g. XXIV yielded 0.066 g. (crude) 17,17a-enol acetate of XXIX, prisms, m. 150.5-52° (methylcyclohexane). XXIX (0.301 g.), m. 155.5-8.5°, and 0.35 cc. SO2Cl2 in 10 cc. CCl4 kept 15 hrs. in the dark at room temperature yielded 0.042 g. 13-Cl derivative (XXXI) of XXIX, prisms, m. 169-70.5° (C6H6-hexane); the mother liquors gave 0.029 g. material, m. 156-8°, possibly the C-13 epimer of XXXI. XXXI (0.046 g.) refluxed 0.5 hr. with 0.4 cc. XXVII gave 0.022 g. XXVII.HCl; the filtrate evaporated and the residual yellow glass triturated with Et2O gave 0.025 g. dl-13,14-dehydro derivative (XXXII) of XXXI, m. 113-23°. Crude XXX (0.619 g.) treated with 3.7 cc. solution of 0.818 g. Br in 10 cc. CCl4, refluxed 10 min. with 6.8 cc. XXVII, and filtered gave 0.420 g. XXVII.HCl; the filtrate evaporated and the residual yellow tacky glass triturated with Et2O gave 0.117 g. XXXII, m. 135-53°, which recrystd. and chromatographed on 2.5 g. Florex yielded 0.001 g. pure XXXII, m. 136-37.5°. XXXII (0.022 g.) and 0.08 g. Na in 1.6 cc. absolute MeOH refluxed 1.5 hrs. under N, concentrated in vacuo, and diluted with Et2O, the solution washed, dried, and evaporated, and the residue triturated with Et2O gave 0.013 g. XXVIII. XXVIII (0.045 g.) and 0.13 g. XXIV in 1.2 cc. xylene refluxed 0.5 hr. under N, cooled, diluted with Et2O, extracted with 10% aqueous NaOH, washed, dried, and evaporated, and the viscous oily residue triturated with Et2O, recrystd. from absolute EtOH, and chromatographed on 1 g. Florex gave 0.0178 g. 8-methoxy-1,2,3,4,5,6-hexahydrochrysene (XXXIII), m. 118-19° (C6H6-hexane); further elution of the chromatogram gave 0.0036 g. XXVIII. Crude XXVIII (6.74 g.) in 460 cc. 95% EtOH containing 0.675 g. NaOH hydrogenated 8 hrs. over 0.675 g. 10% Pd-C at room temperature and about 30 lb., most of the solvent distilled, the residue neutralized with alkali and diluted with C6H6 and Et2O, the solution washed, dried, and evaporated, and the

residual oil crystallized from absolute EtOH gave 4.1 g. dl-8-iso-18-nor-D-homoestrone Me ether (cis-syn-trans-isomer of XXIII) (XXXIV), prisms, m. 137.5-38° (95% EtOH); 2,4-dinitrophenylhydrazone, golden needles, m. 233-4° (CHCl3-EtOH). XXVIII (0.200 g.) in 16 cc. 95% EtOH hydrogenated over 0.100 g. 10% Pd-C until 1 mole equivalent H had been absorbed and the product chromatographed on Al2O3 gave 0.029 g. hydrogenolysis product, 0.094 g. crude XXXIV, and 0.081 g. hydroxylic material, which oxidized with Na2Cr2O7 in AcOH yielded 50% XXVIII, m. 131-6.5°. XXXIV refluxed with NaOMe in MeOH was recovered without change. Furfural (1.2 g.) in 30 cc. 33% aqueous MeOH containing 9 g. NaOH added to 1.75 g. XXXIV in 200 cc. MeOH, kept at room temperature under N, and worked up gave 2.2 g. (crude) 17-furfurylidene derivative (XXXV) of XXXIV, prisms, m. 192-4° (C6H6). XXXV (7.97 g.) and 150 g. MeI added under N with cooling to 20.6 g. K in 700 cc. dry Me3COH, the mixture stirred about 2 hrs., and the crude product (8.6 g.) fractionally crystallized from EtOH gave dl-17-furfurylidene-8-iso-13-iso-D-homoestrone Me ether (γ-1-isomer) (XXXVI) in 2 crops of 5.23 g., m. 164-7°, and 1.23 g., m. 158.5-64°, and 0.61 g. dl-furfurylidene-8-iso-D-homoestrone Me ether (XXXVII) (γ-2-isomer), m. 152-4°. The crude XXXVI chromatographed and recrystd. from EtOH gave pure material, needles, m. 166-7.5° (absolute EtOH); the crude XXXVII purified similarly gave prisms, m. 149-50.5°. XXXVI (0.100 g.) in 10 cc. EtOAc at -70° treated with 1 mole equivalent ozone and evaporated, the residue heated 0.5 hr. on the steam bath with 20 cc. 5% aqueous NaOH and 5 cc. 30% H2O2, and the acidic material isolated in the usual manner yielded 0.087 g. **amorphous** γ-1-diacid (XXXVIII). XXXVIII (0.115 g.) and 0.137 g. PbCO3 pyrolyzed, the pyrolyzate evaporatively distilled at 190°/0.1 mm., the resulting yellow oil dissolved in Et2O, and the Et2O solution washed, dried, and evaporated gave 0.039 g. dl-8-iso-13-isoestrone Me ether (γ-1- **estrone** Me ether) (XXXIX), blades, m. 105-6° (MeOH); also isolated in a form, m. 90.5-1.5°; 2,4-dinitrophenylhydrazone, yellow prisms, m. on the hot stage 180°, resolidified to needles, m. 204-6° (CHCl3-EtOH). XXXIX (0.09 g.) heated 40 min. under N with 2 g. pyridine-HCl at 212-14°, cooled, treated with 5% HCl, and extracted with CHCl3, and the extract worked up gave 0.086 g. dl-8-iso-13-isoestrone, prisms, m. 213.7-15° with sweating at 203° (Me2CO); benzoate, prisms, m. 172-5° with previous sweating at 170° (EtOAc). XXXVII (0.400 g.) ozonized in the same manner and the crude **amorphous** acid (0.300 g.) recrystd. from EtOAc yielded 0.141 g. dl-8-isohomomarrianolic acid Me ether, prisms, m. 214-17° with previous sweating at 198°; the residue from the mother liquors (0.234 g.) treated in the usual manner with 0.30 g. PbCO3 yielded 0.081 g. dl-8-isoestrone Me ether (γ-2- **estrone** Me ether) (XL), blades, m. 152.5-4.5° (MeOH) with previous sweating at 148°; 2,4-dinitrophenylhydrazone, yellow microcrystals, m. 261.5-63° (CHCl3-EtOH) when placed on the hot stage at 257°. XL (0.0500 g.) demethylated with 1 g. pyridine-HCl yielded 0.022 g. dl-8-isoestrone (γ-2- **estrone**) (XLI), prisms, m. 253.6-4.8° (MeOH); benzoate (XLII), prisms, m. 197-8° (MeOH). dl-Equilenin (6.0 g.), m. 281-3°, in 600 cc. 2.5% aqueous KOH hydrogenated at 85° and 2800 lb. initial pressure 4 hrs. at 25° over 24 cc. W-5 Raney Ni and the resulting crude phenolic material (1.19 g.) chromatographed on Al2O3 gave 1.01 g. 8-isoestradiol (XLIII), needles, m. 213.5-14° (MeOH) with a polymorphic transition at 175-95° and softening at 210°, and 3.45 g. neutral material, m. 155-73°, which contained the product of reduction of ring A. 3-Benzoate of XLIII (0.169 g.), m. 179-85° (EtOAc), in 4 cc. pyridine added to 2.5 g. CrO3 in

25 cc. pyridine, kept overnight, diluted with H2O, and extracted with Et2O-C6H6 yielded 0.104 g. XLII, m. 194.5-97° (MeOH); a sample refluxed 2 hrs. with N KOH-MeOH, acidified, and extracted with Et2O gave XLI, m. 152-4.5° (MeOH). XXXIX (16.5 mg.) and 20 mg. 5% Pd-C heated 8 min. under N at 250°, cooled, diluted with C6H6, and filtered, the filtrate evaporated, and the residue triturated with hexane and recrystd. from MeOH gave 6.8 mg. dl-isoequilenin Me ether (XLIV), prisms, m. 125-8°. α-1- **Estrone** Me ether (12.2 mg.) and 20 mg. 5% Pd-C gave similarly 6.0 mg. XLIV, prisms, m. 126-7.3° (MeOH). XXIII (0.05 g.) in 12 cc. MeOH treated with 3 drops furfural and 0.6 cc. 33% aqueous NaOH, seeded after 15 min., and kept 2 hrs. at room temperature gave 0.063 g. 1-oxo-2-furfurylidene-8-methoxy-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysene (XLV), needles, m. 180.8-1.6° (BuOH), also obtained in another form, m. 191-2°; the lower melting form after more than 1 year m. 180-5°. XLV (0.554 g.) in 50 cc. boiling MeOH treated with 0.5 g. NaBH4 in 5 cc. H2O, diluted with 150 cc. H2O, and cooled yielded 0.540 g. (crude) 1-hydroxy-2-furfurylidene-8-methoxy-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysene (XLVI), needles, m. 185-6.5°, blades, m. 186-8° (EtOAc and sublimed at 140°/0.015 mm.). Crude XLVI (2.56 g.), 25 cc. pyridine, and 10 cc. Ac2O refluxed 15 min., poured into ice and H2O, and extracted with CHCl3, and the extract worked up gave 1.94 g. acetate (XLVII) of XLVI, blades, m. 133-5° (Et2O). XLVII saponified with alc. KOH gave 82% XLVI, needles, m. 182-5°. XLVII (0.401 g.) in 25 cc. EtOAc containing 0.12 cc. pyridine ozonized at 170° with 1 mole equivalent ozone, hydrogenated at room temperature and 35 lb. initial pressure over 0.5 g. 6% Pd-SrCO3, filtered, washed, dried, and evaporated, and the residue chromatographed on 25 g. Al2O3 yielded 0.099 g. 2-oxo analog of XLVII, plates, m. 172-5° with sweating at 169° (Me2CO). XLVII (0.505 g.) treated in the usual manner with 1-2 mole equivs. ozone and the crude product chromatographed gave 0.135 g. (crude) 1-acetoxy-2-oxo-8-methoxy-1,2,3,4,4a,5,6,11,12,12a-decahydrochrysene (XLVIII), blades, m. 216.5-17.5 (Me2CO). Br (30.8 mg.) in 2 cc. glacial AcOH added during 20 min. with stirring and cooling to 66.1 mg. XLVIII in 2 cc. glacial AcOH (saturated with dry HBr), the mixture stirred 75 min. at room temperature, diluted with ice and H2O, and extracted with CHCl3, the extracted worked up, and the residue chromatographed on 7.3 g. Al2O3 gave 40.4 mg. oily bromo ketone and 8.9 mg. partially crystalline material (apparently unchanged XLVIII); the NaOH extract acidified and extracted gave 1.9 mg. red waxy material; bromo ketone (39.7 mg.) and 2 g. LiCl in 10 cc. dry HCONMe2 refluxed 10 hrs. under N, cooled, diluted with H2O, and extracted with CHCl3, the extract washed with dilute aqueous NaOH to remove 2.7 mg. acidic material and evaporated, the residual neutral fraction (34.3 mg.) treated with 2 g. LiCl in 10 cc. HCONMe2 during 22 hrs. to give 4.8 mg. acidic material, the remaining neutral fraction (20.3 mg.) dissolved in C6H6 and extracted with Claisen alkali, the extract acidified, diluted with H2O, and extracted with C6H6, the residue from the C6H6 extract (13.9 mg.) heated 20 min. on the steam bath with 7 cc. 30% aqueous KOH and 2.5 cc. Me2SO4, the mixture treated with an addnl. 0.1 cc. Me2SO4, heated 25 min., diluted with H2O, and extracted with C6H6, the extract washed with aqueous NaCl and evaporated, and the semicryst. residue (8.1 mg.) chromatographed on 0.8 g. Al2O3 gave 7.3 mg. cis-2,8-dimethoxy-4b,5,6,10b,11,12-hexahydrochrysene, needles, m. 146-8° (Me2CO), and 1.1 mg. intractable gums; the acidic material (7.5 mg.) treated with Me2SO4 and chromatographed gave 3 mg. unidentified product, m. 125-48°.

L6 ANSWER 23 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1958:45480 CAPLUS
DOCUMENT NUMBER: 52:45480
ORIGINAL REFERENCE NO.: 52:8168d-i,8169a-c
TITLE: Steroid sulfates. I. Some solvolytic reactions of the salts of steroid sulfates
AUTHOR(S): McKenna, Jean; Norymberski, J. K.
CORPORATE SOURCE: Nether Edge Hosp., Sheffield, UK
SOURCE: Journal of the Chemical Society (1957) 3889-93
CODEN: JCSOA9; ISSN: 0368-1769
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
OTHER SOURCE(S): CASREACT 52:45480

AB The pyridinium (I) and K (II) sulfate of cholesterol (III) and pyridinium (IV) and K (V) sulfate of 3β-cholestanol (VI) were converted to their parent alcs. by solvents containing a hetero atom with a relatively readily available lone pair of electrons. Within a group of ethers, increasing basicity of the solvent facilitated the reaction. Solvolysis in ethers was accompanied by the release of 1 equivalent acid; ethanolysis proceeded without change of pH. In dioxane (VII), **estrone** pyridinium sulfate (VIII) was much more readily solvolyzed than the corresponding derivs. of III and VI. III (200 mg.) in 5 ml. CHCl3 shaken 2 hrs. at room temperature with 500 mg. C5H5N-SO3, the excess reagent removed, the residue washed with some CHCl3, the filtrate and washings combined, cooled to 0°, freed from any precipitated material, and hot ligroine added gave I, m. 158-70°, [α]D -27° (c 1.16, all rotations determined in CHCl3 at 15-20°). I gave a pos. halogen test and had an alkali equivalent of 664. For analysis, a sample was recrystd. from CH2Cl2-Me2CO and dried in vacuo 100 hrs. at room temperature In subsequent prepns. filtration through a column of cellulose powder gave good results. I gave II, m. 226-7° (decomposition). VI with C5H5NSO3 gave IV, which dried 24 hrs. at room temperature, m. 165-9°, [α]D 17° (c 0.90). IV gave V, m. 234-5° (decomposition). **Estrone** similarly treated gave VIII, m. 170-5° (CHCl3C6H14), [α]D 84° (c 0.96), giving a pos. test for halogen. The solvents were purified as follows: CHCl3 kept over P2O5, distilled, and refluxed with anhydrous K2CO3; Me2CO refluxed with KMnO4, distilled, and refluxed with anhydrous K2CO3; alc. and VII refluxed with Na; tetrahydrofuran, Et2O, iso-Pr2O, and anisole kept over CaH2; C5H5N kept over KOH. The pyridinium salts of the steroid sulfates were kept in a vacuum desiccator. The composition of each salt was determined before each series of expts. by titration with 0.01N NaOH and (or) by measuring the quantity of the parent alc. obtained by complete cleavage of the salts with hot VII. For each experiment 50-100 mg. of the appropriate salt was taken. The products were identified by m.p. and mixed m.p. I (60 mg.) in 25 ml. Me2CO shaken 20 min. and the solution left 4 days at room temperature gave 89% III; when the solution was heated 5 hrs. III was obtained in theoretical yield. I (138 mg.) in 6 ml. alc. refluxed 3 hrs., the solution cooled, diluted with H2O, and titrated with 0.01N NaOH gave an alkali equivalent identical to that of unchanged material; the usual treatment gave 95% III. II (200 mg.) dissolved rapidly in 10 ml. hot VII gave an **amorphous** precipitate; the mixture refluxed 10 min., diluted with ligroine, and the solids collected gave 52 mg. KHSO4; the filtrate evaporated to dryness gave a residue of 153 mg. III. II (50 mg.) and 20 ml. tetrahydrofuran refluxed 10 min., the KHSO4 removed, and the residue chromatographed on neutral Al2O3 gave 92% III. II (60 mg.) and 10 ml. alc. refluxed 36 hrs. gave 100% III. The experiment repeated but with 75 mg. KOAc gave only a trace of Et2O-soluble

material. II (60 mg.) and 10 ml. H2O refluxed 19 hrs. and the Et2O extract chromatographed on neutral Al2O3 gave 20 mg. III. IV (100 mg.) and 5 ml. alc. refluxed 4 hrs. gave 90% VI, plates, m. 140-2°. In a similar experiment the mixture diluted with H2O and neutralized with 0.01N alkali gave a neutralization equivalent equal to the starting material and extraction with Et2O yielded 85% VI. IV (60 mg.) and 10 ml. MeOH refluxed 20 hrs. gave 86% VI. IV (60 mg.) and 10 ml. H2O heated 19 hrs. gave 18% VI: in a further experiment 70% VI was obtained. In an identical experiment the reaction stopped after 4 hrs. gave only 6% VI, although 0.8 equivalent acid was liberated. V (65 mg.) and 10 ml. VII refluxed 10 min. and neutralized gave 50 mg. VI, m. 139-42°. V (60 mg.) and 10 ml. alc. refluxed 94 hrs. gave 95% VI. Comparison of the ease of solvolysis of I by ethers in CHCl3 established the following order of decreasing activity: VII and tetrahydrofuran > Et2O > iso-Pr2O > anisole. A hypothetical reaction mechanism accounting for the part played by the ethers is given by equations. Ethanolysis is similarly represented. Cleavage of II by refluxing alc. was almost completely suppressed by the addition of KOAc and the pyridinium salts were tenaciously retained on neutral Al2O3.

L6 ANSWER 24 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1957:62265 CAPLUS
DOCUMENT NUMBER: 51:62265
ORIGINAL REFERENCE NO.: 51:11306i,11307a-i
TITLE: Syntheses in the estrogenic hormone group. XV. Reaction of phenylacetylenes with substituted cyclohexanones; a new total synthesis of one racemate of doisynolic acid
AUTHOR(S): Jilek, Jiri O.; Protiva, Miroslav
CORPORATE SOURCE: Pharm. Biochem. Research Inst., Prague
SOURCE: Chemicke Listy pro Vedu a Prumysl (1957), 51, 643-53
CODEN: CLPRAN; ISSN: 0366-6832
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
OTHER SOURCE(S): CASREACT 51:62265

AB cf. C.A. 51, 10393h. Adding the K derivative prepared from 5.1 g. PhC.tplbond.CH and 1.95 g. K in 40 ml. absolute tert-BuOH under stirring to a solution of 9.8 g. Et 2-oxocyclohexylacetate in 40 ml. tert-BuOH, stirring the mixture 5 hrs. at room temperature, decomposing with 5.4 ml. concentrated HCl in 20 ml. H2O, evaporating the solvent, adding 100 ml. H2O, extracting with Et2O, and distilling gave a fraction (3.2 g.), b1.6 185-6°, which yielded, on addition of ligroine, 1.3 g. lactone of 1-phenylethynylcyclohexenol-2-acetic acid (I), m. 116-18°. Hydrogenation of 0.9 g. I over Pd-C with HCO2Na gave lactone of 1-phenethylcyclohexanol-2-acetic acid (II), b0.9 180°. II (1.5 g.) refluxed 6 hrs. with 20 ml. 10% MeOH-KOH on H2O bath gave 1.25 g. 1-phenethylcyclohexanol-2-acetic acid (III), m. 118° (from C6H6-ligroine). III (1.5 g.) heated with 30 ml. 90% H3PO4 45 min. to 110-20° (bath-temperature), poured on ice, extracted with Et2O, and cyclized gave 1.2 g. 1,2,3,4,9,10,11,12-octahydro-1-phenanthrylacetic acid, m. 142°. The analogous reaction of 12.0 g. Et β-(2-oxocyclohexyl)propionate with 6.2 g. PhC.tplbond.CH yielded 8.0 g. lactone of β-(2-phenylethynyl-2-hydroxycyclohexylpropionic acid, b1-5 180-230°, m. 83-4° (from ligroine), which gave, when hydrogenated, 66% lactone of β-(2-phenethyl-2-hydroxycyclohexyl)propionic acid, m. 98° (from ligroine). Similarly was obtained from the Me ester of 2-ethyl-3-methylcyclohexanone-3-carboxylic acid (IV) in 37% yield lactone of 1-phenylethynyl-2-ethyl-3-

methylcyclohexanol-3-carboxylic acid, b0.9 160-80°, m. 90° (from ligroine), which gave, on hydrogenation, lactone of 1-phenethyl-2-ethyl-3-methylcyclohexanol-3-carboxylic acid, b0.2 175-80°. m-MeOC6H4C.tplbond.CH (3.4 g.) allowed to react by similar procedure with 4.8 g. IV gave 2.0 g. fraction, b0.9 160-200°, which was passed over 70 g. Al2O3 to yield in the C6H6-eluate 1.8 g. lactone of 1-(m-methoxyphenylethynyl)-2-ethyl-3-methylcyclohexanol-3-carboxylic acid (V), b0.3 190-205°. V (3.55 g.) hydrogenated in MeOH and the product passed over Al2O3 gave 0.8 g. C6H6 fraction, b0.8 200-15°, and 1.0 g. Et2O fraction, b0.2 190-205°, both containing the lactone of 1-m-methoxyphenethyl-2-ethyl-3-methylcyclohexanol-3-carboxylic acid (VI). The procedure was simplified by leaving out isolation of V to give in 20.4% yield and crystalline form VI, m. 70° (from ligroine-C6H6), besides small amount of 2-ethyl-3-methylcyclohexanone-3-carboxylic acid. VI hydrolyzed by boiling 20 hrs. with 20% MeOH-KOH gave 1-m-methoxyphenethyl-2-ethyl-3-methylcyclohexanol-3-carboxylic acid (VII), m. 103-6° (from ligroine-C6H6). Reducing 5.0 g. VI with 4.0 g. LiAlH4 yielded 3.8 g. 1-m-methoxyphenethyl-2-ethyl-3-methyl-3-hydroxymethylcyclohexanol, b1.5 210-20°, m. 85-7° (from ligroine). Attempts to cyclize VII or VI by means of H3PO4 failed but when the solution of 10.0 g. VI in 130 ml. C6H6 was dropped in the course of 20 min. to a boiling suspension of 29 g. AlCl3 in 250 ml. absolute C6H6 while passing a stream of dry HCl, the mixture refluxed 1 hr. under continued conveying of HCl, left at room temperature overnight, decomposed under cooling with 300 ml. 3N HCl, the C6H6 layer separated and extracted with 600 ml. 5% NaOH, the alkaline solution treated with 50 ml. Me2SO4 after addition of 20 g. NaOH, the resulting mixture heated 1 hr. on H2O bath, cooled, acidified with HCl, the precipitate extracted with Et2O, the extract dried and evaporated, the residue dissolved in 50 ml. Et2O, treated with CH2N2, left overnight, excess CH2N2 decomposed by addition of 4.5 ml. AcOH, Et2O evaporated and the residue distilled, an oily product (6.1 g.) was obtained, b0.08 190, apparently the Me ester of 1-ethyl-2-methyl-7-methoxy-1,2,3,4,9,10,11,12-octahydrophenanthrene-2-carboxylic acid (VIII). An **amorphous** product, m. 50-60°, obtained in 5.60 g. yield by heating 6.1 g. VIII with 24.0 g. KOH, 12 ml. H2O, and 24 ml. EtOH to 180-90°, was dissolved in 5% solution of Na2CO3, evaporated in vacuo to 80 ml., and cooled, the crystalline Na salt (m. 315-25°) acidified, and the separated **amorphous** acid recrystd. from MeOH to give 0.55 g. 7-methyldoisynolic acid (IX), m. 189-91°, apparently identical with the stereoisomer Cα, with configuration cis-anti-cis, of Anner and Miescher (C.A. 42, 1954a; M., C.A. 43, 3085d). IX showed approx. the same biol. activity as **estrone.** Demethylating IX by heating 300 mg. with 3.0 g. C5H5N.HCl 4.5 hrs. to 70-90° gave 105 mg. 1-ethyl-2-methyl-7-hydroxy-1,2,3,4,9,10,11,12-octahydrophenanthrene-2-carboxylic acid, m. 113-17° (from MeOH). The preparation was given of Et β-(m-methoxyphenyl)-α,β-dibromopropionate, m. 58-9° (from ligroine), which was obtained in quant. yield by brominating Et m-methoxycinnamate. Infrared spectra of V and IX were charted.

L6 ANSWER 25 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1957:51924 CAPLUS
DOCUMENT NUMBER: 51:51924
ORIGINAL REFERENCE NO.: 51:9659i,9660a-i,9661a
TITLE: 17-Alkyl-19-nortestosterones
AUTHOR(S): Colton, Frank B.; Nysted, Leonard N.; Riegel, Byron; Raymond, Albert L.

QAZI

CORPORATE SOURCE: G. D. Searle & Co., Chicago
SOURCE: Journal of the American Chemical Society (1957), 79, 1123-7
CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

AB 17-Ethynyl-19-nortestosterone (8.6 g.) in 350 cc. dry dioxane hydrogenated over 1.1 g. 5% Pd-C until 2 moles H were absorbed, filtered, and evaporated to dryness in vacuo, and the residue chromatographed with 20-30% EtOAc in C6H6 on 450 g. silica gel yielded 6.12 g. 17-ethyl-19-nortestosterone (I), m. 137-8° (from aqueous MeOH), [α]D 25° (c 1, CHCl3). A slow stream of C2H2 passed over the surface of a stirred solution of 5.0 g. K in 100 cc. Me3COH and 100 cc. dry Et2O at 0° until saturated, treated with 5.0 g. Me **estrone**, the addition of C2H2 continued 3-4 hrs. at 0°, the mixture kept 18 hrs. at room temperature, treated with 100 cc. 10% aqueous NH4Cl, steam distilled, and filtered, and the residue crystallized from Me2CO gave 5.1 g. 17-ethynylestradiol 3-Me ether (II), m. 150-1.5°. II (5.0 g.) in 75 cc. purified dioxane hydrogenated over 0.5 g. 5% Pd-C until 2 moles H was absorbed, filtered, and evaporated to dryness in vacuo yielded 4.8 g. 17-ethylestradiol 3-Me ether (III), m. 85-7° (from Me2CO-petr. ether). III (4.0 g.) in 100 cc. dry Et2O and 300 cc. liquid NH3 stirred 1 hr. with 4.0 g. Li, treated dropwise during 1.5 hrs. with 30 g. EtOH diluted with an equal volume of dry Et2O while using an addnl. 100 cc. dry Et2O to wash the sides of the flask during the EtOH addition, the NH3 evaporated with gentle warming, the mixture diluted with 100 cc. cold H2O, and the product isolated by extraction gave 3.4 g. 17-ethyl-1,4-dihydroestradiol 3-Me ether (IV), m. 126-8° (from Et2O-MeOH). IV (1.25 g.) in 20 cc. MeOH refluxed 5 min. with 2.2 cc. glacial AcOH and diluted with 100 cc. H2O gave 1.15 g. 17α-ethyl-17-hydroxy-5(10)-estren-3-one, m. 134-6° (from Me2CO-petr. ether). IV (2.0 g.) added with stirring to 2.4 cc. concentrated HCl and 1.6 cc. H2O in 36 cc. MeOH, allowed to stand 2 hrs. at room temperature, and filtered gave 1.7 g. I, m. 136-9° (from Me2CO-petr. ether). 17-Octynylestradiol 3-Me ether (3.0 g.) in 75 cc. purified dioxane hydrogenated over 0.5 g. 5% Pd-C until 2 moles H was absorbed, filtered, and evaporated, and the residue triturated with MeOH gave 1.9 g. 17-octylestradiol 3-Me ether (V), m. 79-81°, [α]D 40° (c 1.25, CHCl3). V (1.5 g.) subjected to a Birch reduction gave 1.2 g. solvated crystalline material which became **amorphous** on drying in vacuo; the **amorphous** material cleaved and isomerized in the usual manner yielded 0.8 g. 17-octyl-19-nortestosterone, m. 120-2° (from aqueous MeOH). II (4.0 g.) reduced in the usual manner yielded 3.1 g. 3-methoxy-19-norpregna-2,5(10),17-(20)-triene (VI), m. 111-12°. VI (1.0 g.) isomerized in the usual manner with HCl gave 0.76 g. 19-norpregna-4,17-(20)-dien-3-one, m. 124-5°. Mg (8.5 g.) (activated with iodine) covered with 200 cc. dry Et2O, treated dropwise with 5.0 g. CH2: CHCH2Br in 20 cc. dry Et2O, and then during 45 min. with 20.0 g. **estrone** Me ether in 95 g. CH2:CHCH2Br and 400 cc. Et2O, refluxed 2.5 hrs., cooled, and treated with 500 cc. 10% aqueous NH4Cl, and the Et2O layer worked up yielded 18.4 g. 17-allylestradiol 3-Me ether (VII), m. 91-1.5° (from Et2O-petr. ether), [α]D 57.4° (c 1.02, CHCl3). VII (11.5 g.) in 200 cc. EtOH hydrogenated over 5 g. 5% Pd-C until 1 mole H had been absorbed, filtered, aad evaporated in vacuo yielded 10.1 g. 17-propylestradiol 3-Me ether (VIII), m. 93-4° (from Et2O-MeOH], [α]D 47.7°. VIII (6.0 g.) reduced with Li in NH3 gave 4.7 g. 17-propyl-1,4-dihydroestradiol 3-Me ether (IX), m. 150-2°, [α]D 105° (c 1.16, CHCl3). VII (5.0 g.) hydrogenated in dioxane over 5% Pd-C yielded 4.0 g. IX, m. 149-51°. IX (1.0 g.) in MeOH heated with glacial AcOH gave 0.8 g.

17α-propyl-17-hydroxy-5(10)-estren-3-one, m. 90.0-1.5°. IX (1.8 g.) cleaved and isomerized in the usual manner yielded 1.4 g. 17-propyl-19-nortestosterone, m. 122-3°, [α]D 21° (c 0.98, CHCl3). 1,4-Dihydroestradiol 3-Me ether (25 g.) in 242 cc. cyclohexane and 860 cc. PhMe refluxed 2 hrs. with 25 g. (iso-PrO)3Al in 347 cc. PhMe, treated dropwise during 10 min. with 169 cc. saturated aqueous Rochelle salt, and steam distilled, the aqueous distillation residue filtered, and the solid product triturated with 100 cc. MeOH and cooled to 0° gave 21.0 g. 1,4-dihydroestrone 3-Me ether (X), m. 141-1.5° (from MeOH). Mg (1.7 g.) (activated with iodine) treated with 9.0 g. CH2:CHCH2Br in 100 cc. Et2O, refluxed 15 min., treated with 2.0 g. X in 100 cc. Et2O, refluxed 1.5 hrs., and treated slowly with 100 cc. 10% aqueous Rochelle salt, the Et2O layer worked up, the residue dissolved in 40 cc. MeOH, 1.5 cc. concentrated HCl, and 5 cc. H2O, kept 2 hrs. at room temperature, and diluted with 200 cc. cold H2O, and the crude precipitate chromatographed on 150 g silica gel yielded 1.1 g. 17-allyl-19-nortestosterone, m. 93-5°. 1-Octyne (24 g.) in 125 cc. dry Et2O stirred 1 hr. at 0° with 7.8 g. EtMe2COK (from 7.8 g. K), treated with 5.7 g. **estrone** Me ether, warmed to room temperature, stirred 24 hrs., and treated with 150 cc. 10% NH4Cl, the organic layer worked up, and the residue chromatographed with 0.5% C6H6 in CHCl3 on silica gel gave 4.6 g. 17-octynylestradiol Me ether, oil. BuLi (from 9.0 cc. BuBr and 0.67 g. Li) added with stirring to 1.65 g. **estrone** Me ether in 40 cc. dry Et2O, stirred 1 hr., decomposed with MeOH and dilute H2SO4, and diluted with Et2O, the Et2O layer worked up, and the residue chromatographed with 20% Skellysolve A in C6H6 on 100 g. Al2O3 gave 426 mg. 17-butylestradiol 3-Me ether (XI), m. 52-5° partially solidified and remelted at 92-4°. XI subjected to a Birch reduction, cleaved and rearranged, and the crude product chromatographed with 20% EtOAc in C6H6 on 35 g. silica gel yielded 118 mg. 17-butyl-19-nortestosterone, m. 126-7° (from aqueous MeOH).

L6 ANSWER 26 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1957:17392 CAPLUS
DOCUMENT NUMBER: 51:17392
ORIGINAL REFERENCE NO.: 51:3638d-i,3639a-i,3640a-b
TITLE: Synthesis of some cyclic acetal and ketal derivatives of some hydroxyl-containing compounds
AUTHOR(S): Petersen, Robert V.; Gisvold, Ole
CORPORATE SOURCE: Univ. of Minnesota, Minneapolis
SOURCE: Journal of the American Pharmaceutical Association (1912-1977) (1956), 45, 572-7
CODEN: JPHAA3; ISSN: 0003-0465
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

AB Dihydropyran (I), anhydro-δ-acetobutyl alc. (II), anhydro-γ-acetopropyl alc. (III), and 3-methyl-2,3-dihydropyran (IV) formed cyclic acetals or ketals with a secondary alc. [cholesterol (V) or other compds.]. I and HO(CH2)4CHO (VI) treated with 2-C10H7SH (VII) gave the same mixed acetal. I, VI, and Ac(CH2)4OH (VIII), AcCH2CH(OH)CH2CH2OH (IX), and Ac(CH2)3OH (X) all reacted with a primary alc. [Prenderol (XI)] to give cyclic acetals and ketals. I, II, and VI also gave the corresponding acetals and ketals with phenols [diethylstilbestrol (XII) and hexestrol (XIII)]. In general, the derivs. of phenols were less stable than the corresponding derivs. of primary and secondary alcs. and the derivs. containing a furanose ring system were less stable than those containing a pyranose ring system. I was purified by the method of Sawyer and Andrus [Organic Syntheses Collective Volume III, 276(1955)] and VI prepared

(Schniepp and Geller, C.A. 40, 71919) from it. VIII was synthesized from AcCHNaCO2Et (XIV) and BrCH2CH2CH2Br (Bergmann and Miekely's modification, C.A. 16, 3874). Controlled heating of VIII to 155-60° dehydrated it to II. II held several days in the presence of acidified water formed a pure grade of VIII. IX was prepared by BzO2H oxidation of II in moist Et2O. X was synthesized from XIV and BrCH2CH2Br [Lipp, Ber. 22, 1196(1889)] except that 2 moles XIV was used and the alkylated acetoacetic ester was heated 12 hrs. with aqueous HCl. X was dehydrated at 207-8° to III. Pure X was obtained by allowing III to remain 1 day in slightly acidulated water. IV was prepared by Parham's method (P. and Holmquist, C.A. 45, 7998c). XI [Et2C(CH2OH)2] (1.32 g.) in 6 cc. CHCl3 treated with 2.10 g. I, then with 1 drop of a 5% solution (XV) of HCl in dioxane (the temperature rose from 24° to 36°), the mixture heated 5 min. at 50°, allowed to cool slowly to room temperature, made slightly alkaline with 0.25 cc. EtOH-KOH, the solvent evaporated, the residue distilled at 150-65°/5 mm., and this fraction redistd. 4 times gave 88% 2,2-diethyl-1,3-bis-(tetrahydro-2-pyranyloxy)propane (XVI), b5 159-64°, also obtained from 1.32 g. XI and 2.55 g. VI under similar conditions. I and V treated by Greenhalgh's method (G., et al., C.A. 46, 2090c) in CHCl3 gave 94.8% 3β-(2-tetrahydro-2-pyranyloxy)-5-cholestene (XVII), also prepared from dioxane in 92.6%, from CH2Cl2 in 89.8%, and from EtOAc in 96.4% yield. V (1.933 g.) and 1.02 g. VI in 7 cc. dioxane plus 1 drop XV heated 1 hr. at 50°, the mixture allowed to cool to 20°, then cooled to 15°, and the crystalline product which separated twice recrystd. from EtOAc gave XVII, m. 157-8.5°, mixed m.p. undepressed. Digitoxin (XVIII) (2. g.) hydrolyzed by Elderfield's method [Advances in Carbohydrate Chemistry, 1, Academic Press, 163(1945)] gave 510 mg. digitoxigenin (XIX), m. 253-5° (from EtOAc). To 100 mg. XIX and 200 mg. I in 1 cc. EtOAc treated with 1 drop of a solution of 1 drop POCl3 in 5 cc. EtOAc, warmed 20 min. at 45°, cooled to room temperature, diluted with 10 cc. petr. ether, and the **amorphous** precipitate crystallized from Et2O-petr. ether, then from anhydrous Et2O, and dried over P2O5 gave 66% 3β-(tetrahydro-2-pyranyloxy)-14β-hydroxy-20(20)-cardenolide, m. 156-90°. XII (805) in 10 cc. dioxane treated with 08.4 g. I then with 1 drop XV warmed 5 min. at 55°, cooled to room temperature, 15 cc. Et2O added, the Et2O solution shaken with 10 cc. of 10% aqueous KOH, the aqueous alkaline solution extracted twice with 20-cc. portions of Et2O, the combined Et2O exts. washed with 20 cc. water, the Et2O removed, and the residue dried over P2O5, recrystd. twice from EtOAc and once from cyclohexane, and dried over P2O5 gave 54.3% α,α'-diethyl-4,4'-bis(tetrahydro-2-pyranyloxy)stilbene (XX), m. 185-8°, also obtained from XII and VI with 1 drop XV. When (1 g.) XIII in 3 cc. warm I was treated with 1 drop POCl3, spontaneous heating occurred and crystals separated from the warm mixture; the mixture heated 5 min. at 60°, cooled, dissolved in 30 cc. EtOAc, and cooled to give 88.8% 1,2-diethyl-4,4'-bis(tetrahydro-2-pyranyloxy)-1,2-diphenylethane, m. 166-9°. VII (6.4 g.), 3.76 g. PhOH, and 3.36 g. I mixed and warmed slightly, 2 drops XV added (spontaneous heating occurred), the mixture extracted after 30 min. with 60 cc. 10% sq. KOH, the aqueous alkaline solution extracted 3 times with 100 cc. portions of Et2O, and the Et2O exts. combined, washed once with water, concentrated, dried over P2O5, distilled, and redistd. 3 addnl. times gave 73.1% 2-naphthyltetrahydro-2-pyranyl sulfide (XXI), b2 180-3°, also obtained from VII and VI with 1 drop XV. **Estrone** (0.27 g.) and 0.5 g. I treated with 1 drop XV, the mixture heated 30 min. at 50°, worked up as in the preparation of XX, and the product recrystd. from EtOAc gave 63.8% 3-(tetrahydro-2-pyranyloxy)-

1,3,5(10)-estratrien-17-one, m. 147-8. Treating XI with II or VIII in the same way as in the preparation of XVI gave 83.5% 2,2-diethyl-1,3-bis(2-methyltetrahydro-2-pyranyloxy)-propane, b6 172-8°. V (1.93 g.) in 8 cc. dioxane and 0.74 g. II treated with 1 drop POCl3, the mixture warmed 15 min. at 50°, cooled about 30 min. (further crystallization occurred at 12°), and the product recrystd. from EtOAc and dried over P2O5 gave 90.4% 3β-(2-methyltetrahydro-2-pyranyloxy)-5-cholestene, m. 174-7°. XIX (0.125 g.) and 0.75 g. II treated with 8 drops of a solution (XXIa) containing 1 drop POCl3 in 10 cc. EtOAc (spontaneous warming and solution occurred), the solution warmed 5 min. at 60°, cooled slowly and the product (further amts. were obtained by addition of Et2O to the mother liquor) recrystd. from cyclohexane gave 80% 3β-(2-methyltetrahydro-2-pyranyloxy)-14β-hydroxy-20(22) -cardenolide (XXII), m. 152-6° (decomposition) (taken on a m.p. block preheated to 145° and the temperature raised 10°/min.); as the temperature was increased, it resolidified and remelted at 253-4°. Digoxin (2 g.) hydrolyzed in a similar manner as XVIII gave 0.575 g. digoxigenin (XXIII), m. 217-19°. XXIII (0.150 g.) and 1.4 g. II treated with 3 drops XXIa, the mixture heated 10 min. at 65°, cooled to room temperature, 30 cc. anhydrous Et2O added, the mixture cooled to 0°, and the product recrystd. twice from anhydrous Et2O gave 62% 3β-(2-methyltetrahydro-2-pyranyloxy)-12β,14β-dihydroxy-20(22)-cardenolide, m. 159-63°. XII in 2 cc. II treated with 1 drop XV, the mixture made alkaline with 2 drops 10% KOH-EtOH after 30 min. at room temperature, diluted with 15 cc. petr. ether, filtered, and the filtrate held 2 days at -5° gave 66.8% of the very unstable α,α'-diethyl-4,4'-bis(2-methyltetrahydro-2-pyranyloxy)stilbene, m. 114-16° (m.p. determined like that of XXII). XIII (1 g.) in 2 cc. II treated with 1 drop of a solution containing 1 drop POCl3 in 5 cc. EtOAc, the mixture heated 10 min. at 55°, and the product isolated like XX and recrystd. from petr. ether gave 63.5% 1,2-diethyl-4,4'-bis(2''-methyltetrahydro-2-pyranylaxy)-1,2-diphenylethane, m. 115-16° (m.p. determined like that for XXII), showing signs of instability. Testosterone (XXIV) (0.150 g.) in 2 cc. CHCl3 and 0.5 g. II treated with 1 drop POCl3 (the mixture heated up spontaneously), 10 cc. petr. ether added after 30 min. at room temperature, the mixture cooled to -5°, and the product recrystd. from EtOAc gave 79% 17β-(2-methyltetrahydro-2-pyranyloxy)-4-androsten-3-one, m. 139-42°. XI (0.66 g.) and 1.32 g. IX warmed on a hot plate until the mixture liquefied, cooled to 40°, 1 drop POCl3 added (spontaneous heating), external heat applied to bring the temperature to 80°, heating continued an addnl. 20 min., and the mixture cooled to room temperature (petr. ether added to the filtrate gave more material) yielded 59% 2,2-diethyl-1,3-bis(2-methyl-3-hydroxytetrahydro-2-pyranyloxy)propane, m. 211-14° (purified by sublimation). XI with III or X treated like XVI gave 2,2-diethyl- 1,3-bis(2-methyltetrahydro-2-furanyloxy)propane. V (1 g.) in 2.b cc. warm X treated with 1 drop XV and warmed 5 min. to 55° gave 83.3% 3β-(2-methyltetrahydro-2-furanyloxy)-5-cholestene, m. 131-5° (from EtOAc and then from petr. ether), mixed m.p. with V depressed to 115-17°. XXIV (0.125 g.) added to 0.6 g. III and 5 drops of a solution containing 1 drop POCl3 in 5 cc. EtOAc gave 74% 17β-(2-methyltetrahydro-2-furanyloxy)-4-androsten-3-one, m. 132-5° (from EtOAc) (on a plate preheated to 125°). V (0.96 g.) in 4 cc. XV with 0.42 g. IV and 1 drop POCl3 gave 3β-(4-methyltetrahydro-2-furanyloxy)-5-cholestene, number m.p. given.

L6 ANSWER 27 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1957:1910 CAPLUS

QAZI

DOCUMENT NUMBER: 51:1910
ORIGINAL REFERENCE NO.: 51:452f-i,453a-c
TITLE: Steroids. LXXX. 1-Methyl-19-nortestosterone and 1-methyl-17α-ethinyl-19-nortestosterone
AUTHOR(S): Ringold, H. J.; Rosenkranz, G.; Sondheimer, Franz
CORPORATE SOURCE: Syntex S.A., Mex.
SOURCE: Journal of the American Chemical Society (1956), 78, 2477-9
CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
OTHER SOURCE(S): CASREACT 51:1910

AB cf. C.A. 50, 13980g. 1-Methylestrone (17 g.) in 250 cc. boiling MeOH and 600 cc. 10% aqueous NaOH treated dropwise during 20 min. with 85 cc. Me2SO4 with stirring, the solution boiled 0.5 hr., diluted with 170 cc. 40% aqueous NaOH, treated dropwise during 20 min. with 85 cc. Me2SO4, boiled 1 hr., cooled, and diluted with 200 cc. H2O gave 15.0 g. 1-methylestrone Me ether (I), m. 129-30° (from Me2CO-hexane), [α]D 238°. Liquid NH3 (2 l.) carefully added to 13 g. I in 1 l. dry propylene glycol mono-Me ether, the mixture treated during 20 min. with stirring with 25 g. Li wire, the reaction allowed to proceed 2 hrs., the mixture diluted with 5 l. H2O, the precipitate dissolved in hot C6H6, the solution washed, dried, and evaporated, the crude residual enol ether heated 15 min. at 60° with 500 cc. MeOH and 400 cc. 3N HCl, the mixture diluted with H2O and extracted with EtOAc, and the extract worked up gave 5.4 g. 1-methyl-19-nortestosterone (II), m. 205-7°, [α]D 43°; the mother liquors chromatographed several times on silica gave an **amorphous** product which could not be crystallized and is probably enriched in the C-1 isomer of II. II (100 mg.) in 5 cc. glacial AcOH treated 1 hr. with 50 mg. CrO3 in 1 cc. H2O, diluted with H2O, and extracted with EtOAc gave 75 mg. 1-methyl-19-nor-4-androstene-3,17-dione, m. 192-5°, [α]D 132°. **Estrone** Me ether subjected to a Birch reduction, the resulting crude enol ether (19.8 g.) boiled 20 hrs. with 400 cc. C6H6 and 70 cc. (CH2OH)2 in the presence of 4.4 g. p-MeC6H4SO3H with continuous removal of the H2O, the mixture treated with aqueous Na2CO3, the organic layer washed, dried, and evaporated, and the residual, crude, **amorphous** product (21.4 g.) dissolved in 200 cc. dry pyridine, the solution cooled, treated gradually under N with stirring and cooling with 21.4 g. CrO3, kept 20 hrs. at room temperature, diluted with EtOAc, and filtered through celite-Al2O3, the filtrate evaporated, the residual 3-cycloethylene ketal of 19-nor-4-androstene-3,17-dione (18.3 g.), oil, dissolved in 400 cc. dry PhMe, and treated with 18.3 g. K in 430 cc. Me3COH, the air displaced by N, the mixture treated at room temperature 20 hrs. with a stream of dry, purified C2H2, diluted with H2O, acidified with HCl to pH 1, steam distilled to remove the organic solvents, and cooled, and the crystalline deposit isolated gave 9.46 g. 17α-ethinyl-19-nortestosterone (III), m. 201-4°, [α]D -24°; the mother liquors chromatographed on Al2O3 gave an addnl. 1.07 g. III, m. 202-5°. I (7 g.) subjected to a Birch reduction, the resulting unhydrolyzed enol ether carried through the stages of ketalization, CrO3-pyridine oxidation, C2H2 condensation, and acid hydrolysis, and the final product chromatographed on silica gave the 1-Me derivative of III, m. 196-7°. 1,4-Dihydroestradiol Me ether (IV) (300 mg.) in 3 cc. pyridine oxidized with 300 mg. CrO3 gave 0.21 g. **estrone** Me ether, m. 166-8°. IV (0.5 g.) in 5 cc. pyridine and 0.5 cc. H2O treated 2 hrs. at 20° with AcNHBr gave a product in which ring A had

aromatized (85%). IV (0.5 g.) refluxed 2 hrs. with 20 cc. PhMe, 0.25 g. (iso-PrO)3Al, and 5 cc. cyclohexanone gave material which was aromatized (45%).

L6 ANSWER 28 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1956:44974 CAPLUS
DOCUMENT NUMBER: 50:44974
ORIGINAL REFERENCE NO.: 50:8751i,8752a
TITLE: Ephedrine salts of steroid 3-monosulfates
INVENTOR(S): Glen, Wm. L.; Barber, Richard J.
PATENT ASSIGNEE(S): Ayerst, McKenna & Harrison, Ltd.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 489775		19530120	CA	

AB Ephedrine-HCl (1.25 g.) in 8 ml. H2O added to 2 g. Na **estrone** sulfate in 50 ml. H2O, the solution chilled, and the white crystalline ephedrine (I) **estrone** sulfate collected, washed with H2O, dried in vacuo over P2O5, and recrystd. from MeOH gives needles, m. 207°, **estrone** content 50.3%. Similarly prepared are: I equilin sulfate m. 200-5°; I equilenin sulfate m. 195-205°; the I salt with water-soluble conjugated estrogens from mare's urine, a buff-colored powder; I β-estradiol 3-monosulfate, a white **amorphous** powder. The stable addition products exhibit vasoconstricting activity.

L6 ANSWER 29 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1955:73721 CAPLUS
DOCUMENT NUMBER: 49:73721
ORIGINAL REFERENCE NO.: 49:14045d,14046a-d
TITLE: Cyanohydrins of steroid ketones
INVENTOR(S): Ercoli, Alberto; Justoni, Romeo
PATENT ASSIGNEE(S): Francesco Vismara Societa per azioni
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 712873		19540804	GB 1952-19156	19520729

AB Steroid ketones with a large excess of the cyanohydrin of a carbonyl compound of low mol. weight give the steroid cyanohydrin. The reaction is reversible and the steroid ketone can be regenerated by heating the cyanohydrin with an excess of the carbonyl compound, usually in the presence of a basic catalyst. The **amorphous**, neutral material (40 g.) from the oxidation of cholesteryl acetate dibromide, followed by debromination and hydrolysis, and 35 cc. Me2C(OH)CN (I) in 50 cc. EtOH warmed 30 min. give 10 g. dehydroepiandrosterone cyanohydrin (II) (mixture of epimers). The old methods with anhydrous HCN, or KCN with AcOH or HCl, give a mixture of II and 5-pregnen-3β-ol-20-one cyanohydrin (III). I (575 cc.), 2.17 g. KCN in 5 cc. H2O, and 288.4 g. pure dehydroepiandrosterone (IV) in 2.5 l. EtOH agitated 20 min. give 90% II, m. 170-210°. NH4OH (100 cc. 0.01 N) added to 31.5 g. II in 350 cc. boiling Me2CO, and 100 cc. H2O added after 1 hr., gives 24 g. IV, m. 146°. Similarly are prepared in 80-100% yield the cyanohydrins of

the following ketones (mixture of epimers), which are subsequently converted back to the parent ketone (m.p. cyanohydrin given): dehydroepiandrosterone acetate, m. 160-80°; III, m. 190-200°; mixture of androsterone and etiocholan-3α-ol-17-one (3.6 g. from 16 g. ketonic, unsaponifiable fraction from male urine); epiandrosterone (from oxidized dihydrocholesterol acetate), m. 175-80°; androstan-17β-ol-3-one, m. 195-205°; etiocholane-3,17-dione (dicyanohydrin) (from degradation of dehydrolithocholic acid), m. about 92° (decomposition); androstane-3,17-dione, m. 158° (decomposition); **estrone**, m. 198-9° (decomposition). Other cyanohydrins, e.g., those of AcEt, Et2CO, HCHO, AcH, EtCHO, cyclopentanone, cyclohexanone, etc., can be used in place of I.

L6 ANSWER 30 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1954:49496 CAPLUS
DOCUMENT NUMBER: 48:49496
ORIGINAL REFERENCE NO.: 48:8804e-i,8805a-i,8806a-i,8807a-i,8808e-f
TITLE: Constituents of the adrenal gland and related compounds. LXXXV. Partial synthesis of cortisone and related compounds from sarmentogenin
AUTHOR(S): Lardon, A.; Reichstein, T.
CORPORATE SOURCE: Univ. Basel, Switz.
SOURCE: Pharmaceutica Acta Helvetiae (1952), 27, 287-302
CODEN: PAHEAA; ISSN: 0031-6865
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB cf. C.A. 45, 8025i. Sarmentogenin (1.22 g.) was acetylated by the method of Katz (C.A. 42, 6832f) to 1.54 g. crude diacetate (I), fine needles, m. 145-65° (all m.p. are corrected). The crude I in 50 cc. pure AcOEt was treated 0.5 hr. at -80° with about 100 cc. O containing 4% O3/min., the blue solution let stand at -80°, evaporated in vacuo at 30°, the residue dissolved in 6 cc. glacial AcOH, shaken about 1 hr. at 20-30° with small portions Zn dust, the mixture filtered, the filter residue washed with Et2O, the washing combined with the filtrate, evaporated in vacuo, the residue taken up in 1:3 CHCl3-Et2O, and the solution washed with dilute HCl, aqueous Na2CO3, and H2O, dried with Na2SO4, and evaporated to give
60 mg. acidic product and 1.58 g. crude neutral product, which was dissolved in 100 cc. MeOH, let stand 16 hrs. at 20° with 1.2 g. KHCO3 in 35 cc. H2O, and worked up in the usual manner to yield 1.39 g. crude 3β,11α-diacetoxy-14,21-dihydroxy-14β-pregnan-20-one (II), colorless foam; the alkaline washings yielded 70 mg. acidic products. II (228 mg.) in 1.5 cc. pyridine and 1 cc. Ac2O let stand 4 hrs. at 18° and then heated 3 hrs. at 60° yielded 252 mg. crude 3β,11α,21-triacetoxy-14-hydroxy-14β-pregnan-20-one (III), reducing alkaline Ag-diammine solution in MeOH rapidly at 20°. Crude III (250 mg.) chromatographed on activated Al2O3 and the column eluted with petr. ether-C6H6, C6H6, and C6H6-Et2O (9:1) yielded 210 mg. pure III, m. 86-90° (from petr. ether at 0°), [α]17D 31.7 ± 2° (c 1.260, CHCl3). Crude III in 3 cc. pyridine heated 16 hrs. at 70° with 0.6 cc. POCl3 and 0.02 cc. H2O, the mixture treated with ice, extracted with Et2O, the extract washed, worked up, the crude product (180 mg.) in pure C6H6 filtered through 2 g. Al2O3, the filtrate evaporated, the light-colored sirup (174 mg.) dissolved in 5 cc. glacial AcOH, hydrogenated 1.5 hrs. over 40 mg. PtO2.H2O, the mixture filtered, the filter residue washed with CHCl3 and Et2O, the filtrate evaporated, the residue dissolved in 2 cc. glacial AcOH, and the solution let stand 16 hrs. at 18° with 1.5 cc. 2% CrO3-AcOH solution and worked up gave 77 mg. 3β,11α,21-triacetoxy-20-pregnanone (IV), colorless prisms, m. 177-81° (from Et2O-petr. ether); the mother liquor (86 mg.)

chromatographed on Al2O3 gave an addnl. 5 mg. IV; total yield 34.5%. The remaining mother liquor (81 mg.) in 10 cc. MeOH let stand 48 hrs. at 20° with 150 mg. KHCO3 in 3 cc. H2O, the mixture worked up with CHCl3-Et2O, the crude product (78 mg.) treated in dioxane with aqueous HIO4, the resulting crude acid (45 mg.) treated with CH2N2, and the Me ester mixture (47 mg.) acetylated and chromatographed yielded a few mg. Me 3β,11α-diacetoxy-14β-etiocholanate (V), m. 136-8°, and 24 mg. Me 3β,11α-diacetoxy-14-hydroxy-14β-etiocholanate (VI). II (1.39 g.) in 15 cc. dioxane let stand 5 hrs. at 20° with 1.8 g. HIO4 in 5 cc. H2O, and the mixture worked up with CHCl3 and separated with Na2CO3 gave 220 mg. neutral product and 1 g. crude acid which with CH2N2 yielded 760 mg. VI, m. 162-5° (from Me2CO-petr. ether). VI (760 mg.) in 6 cc. dry pyridine heated 16 hrs. with 2.4 cc. POCl3 and 0.1 cc. H2O at 60°, and the mixture treated with ice and worked up gave 790 mg. crude product which distilled at 170° (bath temperature)/0.01 mm. yielded 586 mg. Me 3β,11α-diacetoxy-14-etiocholenate (VII), colorless plates, m. 114-20° (from petr. ether), [α]17D 7.3 ± 1° (c 2.049, CHCl3), giving a pos. C(NO2)4 test; chromatographed on Al2O3 and eluted with petr. ether-C6H6, it yielded colorless platelets, m. 102-4°, [α]16D 4.0 ± 1.5° (c 1.503, CHCl3); the portions eluted somewhat later gave colorless rhombohedrons, m. 145-55°. VII (720 mg.) in 15 cc. glacial AcOH hydrogenated 1 hr. over 70 mg. PtO2.H2O gave 720 mg. crude product which, on fractional crystallization from Et2O-petr. ether yielded 510 mg.

Me 3β,11α-diacetoxyetiocholanate (VIII), m. 170-80°, and 21 mg. V, m. 136-9°; the mother liquors chromatographed on 6 g. Al2O3 gave 27 mg. VIII and 123 mg. V; the crude V recrystd. from Et2O-petr. ether gave the pure product, needles, m. 138-41°, [α]17D 43.3 ± 2° (c 1.478, CHCl3). VIII (610 mg.), m. 175-9°, refluxed 3 hrs. with 1 g. KOH in 15 cc. MeOH, the mixture diluted with H2O, the MeOH removed in vacuo, the alkaline solution washed with CHCl3, the aqueous layer acidified with HCl, extracted with CHCl3, and the extract washed with H2O, dried, and evaporated yielded 463 mg. crude 3β,11α-dihydroxyetiocholanic acid (IX), recrystn. from CHCl3-Et2O gave 427 mg. colorless crystals, m. 236-40°. IX (415 mg.), m. 236-40°, in 3 cc. dry pyridine and 2 cc. Ac2O let stand 16 hrs. at 20°, heated 2 hrs. at 60°, then 1.5 hrs. with 2 cc. H2O at 100°, acidified with dilute HCl, extracted with CHCl3-Et2O, and the extract washed with dilute HCl and H2O, dried, and evaporated yielded 515 mg. crude product, recrystd. from CHCl3-Et2O to give 496 mg. 3β,11α-diacetoxyetiocholanic acid (X), needles, m. 245-50°, [α]17D 22.1 ± 1.5° (c 1.444, CHCl3). X (225 mg.) dried by evaporating with C6H6, let stand with 1.5 cc. pure SOCl2 16 hrs. at 18°, the mixture evaporated in vacuo, the residue evaporated twice more with a little C6H6, dissolved in C6H6, treated with 300 mg. CH2N2 in dry C6H6, the mixture let stand 3 hrs. at 18°, evaporated in vacuo, the crude residue (240 mg.) chromatographed on 6 g. Al2O3, the column eluted with petr. ether-C6H6 and C6H6, and the resulting purified product recrystd. from Et2O-petr. ether yielded 195 mg. 3β,11α-diacetoxy-21-diazopregnan-20-one (XI), light yellow prisms, m. 157-8° (decomposition), [α]18D 106.4 ± 2° (c 1.268, CHCl3); a few crystals, m. 190-205°, eluted with C6H6-Et2O, were discarded. XI (40 mg.) in 1 cc. glacial AcOH heated 0.5 hr. at 100-5°, the mixture evaporated in vacuo, the crude product (42 mg.) recrystd. from Me2CO-Et2O, and the resulting crystalline solid (34 mg.), m. 175-80°, recrystd. from Me2CO-Et2O gave 3β,11α,21-triacetoxy-20-pregnanone (IV), colorless prisms, m. 178-81°,

[α]18D 60.2 ± 2° (c 1.393, CHCl3). XI (200 mg.) let stand 16 hrs. at 23° with 150 mg. KOH in 3 cc. MeOH, the mixture diluted with H2O, the free alkali neutralized with KHCO3, the MeOH removed in vacuo, the residue extracted with CHCl3, passed through Al2O3, heated 0.5 hr. at 100-5°, the mixture evaporated in vacuo, the residue chromatographed on 4 g. Al2O3, and the product (60 mg.) eluted with C6H6 recrystd. from Et2O-petr. ether gave 20 mg. 3β-hydroxy-11α,21-diacetoxy-20-pregnanone (XII), colorless needles, m. 139-40°, [α]18D 52 ± 2° (c 1.000, CHCl3) (it is postulated that the 3β-AcO group of IV was saponified); the Al2O3 column eluted with C6H6-Et2O gave 81 mg. crude 3β,11α-dihydroxy-21-acetoxy-20-pregnanone (XIII), oil. XIII (81 mg.) in 1.5 cc. glacial AcOH treated dropwise with 2 cc. 2% CrO3-AcOH solution and the mixture let stand 3 hrs. at 20° gave 77 mg. crude product which, chromatographed on Al2O3, yielded 38 mg. 21-acetoxy-3,11,20-pregnanetrione, fine needles, m. 154-7° (from Et2O-petr. ether), [α]18D 109.9 ± 2° (c 1.182, CHCl3). XI (50 mg.) in 1 cc. glacial AcOH treated similarly with 0.6 cc. 2% CrO3-AcOH solution gave 47 mg. crude, and, when chromatographed, 25 mg. pure 11β,21-diacetoxy-3,20-pregnanedione (XIV), colorless needles, m. 141-3° (from Et2O-petr. ether), [α]18D 69.1 ± 3° (c 0.752, CHCl3). XIV (88 mg.), m. 138-40°, in 0.5 cc. glacial AcOH treated dropwise with 33 mg. Br in 0.41 cc. glacial AcOH gave 109 mg. crude bromide; this treated in AcOH with H2NCONHNH2.HCl, NaOAc, H2O, and AcOH under N at 65°, and the mixture heated with AcCO2H, NaOAc, and H2O at 75-80° yielded 87 mg. Br-free product. The Br-free product let stand 16 hrs. at 20° with 0.2 cc. dry pyridine and 0.1 cc. Ac2O, the resulting crude product (87 mg.) chromatographed on 3 g. Al2O3, and the column eluted with petr. ether-C6H6 and pure C6H6 gave 55 mg. product which after seeding (seed crystals obtained from 1 of the fractions after standing several weeks) yielded 22 mg. 11-epicorticosterone diacetate (XV), m. 138-43°; analytical sample, m. 143-5°, [α]18D 156.3±2° (c 1.305, CHCl3), forming in concentrated H2SO4 a light yellow solution with greenish fluorescence on a black background. Sarmentogenin dibenzoate (1.42 g.), m. 280-5°, ozonized in 100 cc. EtOAc, the ozonide reduced with Zn dust, the neutral product (1.54 g.) in 150 cc. MeOH let stand 48 hrs. with 1.2 g. KHCO3 in 50 cc. H2O, and the mixture concentrated in vacuo gave 1.34 g. crude 3β,11α-dibenzoyloxy-14,21-dihydroxy-14β-20-pregnanone (XVI), m. 190-8°, recrystg. from Me2CO-Et2O in colorless granules, m. 200-3°, [α]16D 3.5±2° (c 1.109, CHCl3); an addnl. 40 mg. crude XVI was extracted from the mother liquors with CHCl3-Et2O. XVI (1.38 g.) treated 16 hrs. at 23° with 5 cc. pyridine and 4 cc. Ac2O gave 1.510 g. crude 21-acetoxy-3β,11α-dibenzoyloxy-14-hydroxy-14β-20-pregnanone (XVII), which, recrystd. from Et2O-MeOH, gave the pure material, colorless plates, m. 142-50°, [α]18D 12.4±1.5° (c 1.612, CHCl3). XVII(430 mg.), m. 130-40°, in 5 cc. pyridine heated 3 days with 1.2 cc. POCl3 and 0.02 cc. H2O at 60°, and the mixture treated with ice and worked up yielded 355 mg. crude unsatd. ketonic intermediate, which, hydrogenated 5 hrs. in 10 cc. EtOAc and 0.5 cc. glacial AcOH over 60 mg. PtO2.H2O, gave 355 mg. crude product; this treated 8 hrs. in 3 cc. glacial AcOH with 3 cc. 2% CrO3-AcOH solution, and the resulting crude product (330 mg.) chromatographed on 10 g. Al2O3 and eluted with petr. ether-C6H6 gave 150 mg. crystals melting unsharply; the column eluted further with petr. ether-C6H6 and pure C6H6 yielded 100 mg. product giving on recrystn. from Me2CO-petr. ether 70 mg. 21-acetoxy-3β,11α-dibenzoyloxy-20-pregnanone (XVIII), colorless flat needles, m. 197-200°, [α]18D 34.6±2° (c 1.068, CHCl3). XVI (105 mg.), m. 200-3°, in 3 cc. dioxane let stand 6 hrs. at 20° with 120 mg. HIO4 in 1 cc. H2O gave 101 mg. crude, and,

recrystd. from Et2O-petr. ether, 84 mg. pure 3β,11α-dibenzoyloxy-14-hydroxy-14β-etiocholanic acid (XIX), colorless needles, m. 255-9°. XIX (78 mg.) with CH2N2 in Et2O yielded 72 mg. Me ester (XX), colorless needles, m. 217-18°, [α]18D 7.6±2° (c 1.175, CHCl3). XX (67 mg.) in 1 cc. dry pyridine heated 16 hrs. at 60° with 0.3 cc. POCl3 and 0.01 cc. H2O, the resulting crude oily product chromatographed on 2 g. Al2O3, the purified fractions (41 mg.) hydrogenated in 5 cc. EtOAc and 0.1 cc. AcOH over 12.5 mg. PtO2.H2O, and the resulting product chromatographed on 2 g. Al2O3 and then recrystd. from MeOH and from Et2O-petr. ether gave Me 3β,11α-dibenzoyloxyetiocholanate (XXI), m. 133-40°, [α]16D 6.1 ± 4° (c 0.490, CHCl3). VIII saponified, methylated, and then benzoylated gave XXI, needles, m. 130-40°, [α]17D 5.5 ± 4° (c 0.543, CHCl3). XVIII (85 mg.) in 40 cc. MeOH and 10 cc. dioxane let stand 5 days at 20° with 200 mg. KHCO3 in 12 cc. H2O, the mixture worked up with CHCl3, the crude product (78 mg.) in 3 cc. dioxane let stand 5 hrs. at 20° with 100 mg. HIO4 in 1 cc. H2O, and the mixture worked up yielded 4 mg. neutral product and 75 mg. crude acid, m. 162-70° with conversion to prisms, m. 252-60° (from Me2CO-petr. ether); the crude acid (75 mg.) refluxed 2.5 hrs. in 5 cc. MeOH with 400 mg. KOH in 1 cc. H2O, the mixture worked up, and the resulting crude acid mixture (77 mg.) treated with CH2N2 and then with pyridine-Ac2O yielded 39 mg. Me 3β-acetoxy-11β-benzoyloxyetiocholanate, needles, m. 242-7° (from CHCl3-petr. ether), [α]17D 13.2 ± 3° (c 0.684, CHCl3); the residue recrystd. from Me2CO-petr. ether yielded 21 mg. VIII, m. 175-8°. IV (850 mg.) in 50 cc. absolute EtOH and 9.5 cc. glacial AcOH shaken 4 hrs. at 20° with 9.5 g. finely powdered KCN, the mixture diluted with 2 cc. glacial AcOH and 200 cc. H2O, extracted with Et2O after removal of the EtOH, the extract washed with dilute HCl and H2O, dried, evaporated, the residue dissolved in 8 cc. dry pyridine, treated 16 hrs. at 35° and 6 hrs. at 40° with 1.6 cc. POCl3, the resulting crude product (900 mg.) chromatographed on 30 g. Al2O3, the column eluted with petr. ether-C6H6 (up to 50% C6H6 content) gave 270 mg. recovered IV and then eluted with C6H6-petr. ether and C6H6-Et2O gave 492 mg. product, which, recrystd. from Et2O-petr. ether, yielded 334 mg. 3β,11α,21-triacetoxy-17-pregnen-20-yl cyanide (XXII), m. 144-50°; the mother liquors (158 mg.) consisted of crude XXII, usable for further reaction; an analytical sample, m. 150-6°, [α]18D -15.8 ± 2.0° (c 1.013, CHCl3), was obtained by repeated crystallization from Et2O-petr. ether as colorless platelets, λEtOHmax. 223 mμ (log ε 4.07), 282 (1.29). XXII (215 mg.), m. 144-50°, in 10 cc. MeOH let stand 24 hrs. at 20° with 0.35 cc. H2O, the mixture diluted with H2O, extracted, after removal of the MeOH in vacuo, with 4 portions of CHCl3, and the extract washed with little H2O, dried, and evaporated gave a 125 mg. mixture (XXIIA) of 3β,11α,21-trihydroxy-17-pregnen-20-yl cyanide (XXIII) and its 11α-AcO derivative (XXIV), **amorphous** powder; the aqueous alkaline solution acidified to Congo red with HCl, extracted with CHCl3, the extract washed with H2O, dried, evaporated, the residue (47 mg.) treated with CH2N2 in Et2O, the mixture of the resulting Me esters acetylated with pyridine-Ac2O, and the crude product (49 mg.) recrystd. from Et2O-petr. ether yielded 29 mg. VIII, m. 174-8°. XXII (294 mg.) in 10 cc. MeOH let stand 16 hrs. at 20° with 700 mg. KOH in 0.7 cc. H2O gave similarly a mixture (XXIVA) of 164 mg. neutral and 75 mg. acidic products. XXII (130 mg.) in 25 cc. 1% HCl in MeOH let stand 16 hrs. at 30°, the mixture concentrated in vacuo, diluted with H2O, extracted with Et2O-CHCl3, and the extract washed with aqueous Na2CO3 and H2O, dried, and evaporated gave 104 mg. crude XXIV, colorless foam. XXIIA (27 mg.) in 0.2 cc. pyridine and 0.1 cc. Ac2O let stand 16 hrs. at

20° and heated 2 hrs. at 50° yielded 30 mg. crude and 22 mg. purified XXII. XXIVA (164 mg.) dried by evaporating with C6H6 in vacuo, dissolved in 3 cc. dioxane, and let stand 16 hrs. at 0° with 0.15 cc. pyridine and 0.10 cc. Ac2O gave 181 mg. crude mixture of 21-acetoxy (XXV) and 11α,21-diacetoxy derivative (XXVI) of XXIII, which, let stand in 2 cc. C6H6 and 0.08 cc. pyridine 16 hrs. at 20° with 200 mg. OsO4, the mixture concentrated in vacuo to 1 cc., shaken with 5 cc. EtOH and 0.5 g. Na2SO3 in 5 cc. H2O 4 days at 20°, filtered, the filtrate acidified with AcOH, freed from EtOH in vacuo, extracted with CHCl3, the extract washed with H2O, dried, and evaporated, the residue (111 mg.) dissolved in little Me2CO, diluted with Et2O, filtered, and the filtrate evaporated gave 101 mg. residue; 112 mg. crude mixture of XXV and XXVI obtained from **amorphous** XXII gave similarly 68 mg. residue; the residue (169 mg.) dried with C6H6 in vacuo and acetylated in dioxane gave 183 mg. crude product which was chromatographed on Al2O3; the column eluted with C6H6 containing 10% Et2O gave only 15 mg. **amorphous** product; subsequent elution with C6H6 containing 20% Et2O gave 30 mg. crude and 11 mg. pure 11α,21-diacetoxy-3β,-17-dihydroxy-20-pregnanone (XXVII), m. 222-5°; further elution with C6H6-Et2O and Et2O gave 68 mg. crude 21-acetoxy-3β,11α,17-trihydroxy-20-pregnanone (XXVIII), colorless resin, [α]18D 32.8° ± 1° (c 2.134, Me2CO). XXVII (8 mg.) in 0.2 cc. glacial AcOH let stand 8 hrs. at 20° with 0.1 cc. 2% CrO3 in AcOH, and the mixture treated with 0.1 cc. MeOH and let stand 6 hrs. yielded 8 mg. 11α,21-diacetoxy-17-hydroxy-3,20-pregnanedione (XXIX), colorless platelets, m. 222-6° (from Me2CO-petr. ether), light yellow in concentrated H2SO4, [α]18D 34.8 ± 2° (c 1.073, Me2CO). XXVIII in 0.5 cc. glacial AcOH treated portionwise within 6 hrs. with 1.7 cc. 2% CrO3 in AcOH, and the mixture let stand 2 hrs., and then 5 hrs. with 0.1 cc. MeOH gave 54 mg. neutral product which, chromatographed on 2 g. Al2O3, and eluted with C6H6-petr. ether gave 9 mg. crystalline product, m. 178-80° (from Et2O-petr. ether), with C6H6 and C6H6-Et2O (95:5) 18 mg. XXIX, and with C6H6-Et2O 18 mg. 21-acetoxy-17-hydroxy-3,11,20-pregnanetrione (XXX), m. 220-8° (from Me2CO-petr. ether). The mixture of XXIII and XXIV (125 mg.) partially acetylated, the resulting mixture (130 mg.) of XXV and XXVI in 1.5 cc. absolute C6H6 and 0.06 cc. pyridine treated with 135 mg. OsO4, diluted with CHCl3, washed with H2O, dried, evaporated in vacuo, the violet-brown residue dissolved in 3 cc. glacial AcOH, treated portionwise 2 hrs. with 4 cc. 2% CrO3 in AcOH, the mixture worked up in the usual manner with CHCl3, the crude brown product (220 mg.) dissolved in 5 cc. EtOH, shaken 48 hrs. at 20° with 0.3 g. Na2SO3 in 5 cc. H2O, the mixture worked up in the usual way, the resulting crude product (80 mg.), m. 208-20°, acetylated with 0.5 cc. pyridine and 0.3 cc. Ac2O, the crude acetate (89 mg.) chromatographed on 2 g. Al2O3, and the column eluted with C6H6 and C6H6-Et2O (up to 10% Et2O content) gave 10 mg. crude XXIX, m. 216-26° (recrystd., m. 222-6°); further elution with C6H6-Et2O gave 44 mg. crude and 22 mg. purified XXX, m. 226-9° (from Me2CO-Et2O), [α]19D 81.2 ± 3° (c 0.616, Me2CO).

Crude XXII (104 mg.) partially acetylated, the resulting crude monoacetate (112 mg.) in 1.5 cc. dry C6H6 and 0.06 cc. pyridine treated with 130 mg. OsO4, the product in 4 cc. AcOH treated portionwise with 2 cc. 2% CrO3 in AcOH, let stand 3 hrs., worked up in the usual manner, the crude oxidation product (245 mg.) chromatographed on Al2O3, all fractions (**amorphous**) (200 mg.) reduced with Na2SO3, worked up, acetylated, the crude product (90 mg.) chromatographed on 3 g. Al2O3, and the column eluted with C6H6 gave 8 mg. **amorphous** material; elution with C6H6-Et2O gave then 60 mg. crude or 23 mg. pure XXIX, m. 220-7°, a similar run with 125 mg. crude **amorphous** XXII gave 20 mg. crystalline

XXIX. XXX (36 mg.), m. 226-9°, in 0.5 cc. glacial AcOH treated slowly with 14.6 mg. Br in 0.18 cc. glacial AcOH yielded 27 mg. bromide, m. 206-10° (decomposition) (from Me2CO-Et2O); the mother liquor debrominated with Zn dust in AcOH at 30° gave 8 mg. recovered XXX; the crystalline bromide, (27 mg.) in 1.5 cc. glacial AcOH heated 2 hrs. at 65° under N with 24 mg. H2NCONHNH2.HCl, 36 mg. NaOAc, 0.1 cc. H2O, and 4 cc. AcOH, and the mixture treated with 0.3 cc. AcCO2H, 80 mg. NaOAc.3H2O, and 0.6 cc. H2O, heated 1.5 hrs. at 70°, then 1.25 hrs. at 80°, cooled, let stand 16 hrs. at 20° with 0.1 cc. AcCO2H, and worked up in the usual manner with CHCl3-Et2O yielded 17 mg. crude neutral product giving on recrystn. from Me2CO-Et2O 4 mg. pure cortisone acetate (XXXI), m. 232-8°, [α]18D 168.8 ± 4° (c 0.459, Me2CO); the mother liquor chromatographed on 1 g. Al2O3 and eluted with C6H6-Et2O and Et2O gave an addnl. 3 mg. XXXI. XXIX (40 mg.), m. 214-15°, in 0.5 cc. glacial AcOH treated dropwise with 80 mg. Br in 0.19 cc. AcOH and the mixture worked up as for XXXI gave 33 mg. crystalline bromide, m. 223-30°, which was further treated as described for XXXI to yield 14 mg. 11α,21-diacetoxy-17-hydroxy-4-pregnene-3,20-dione, m. 201-6°, [α]17D 99.7 ± 3° (c 0.852, Me2CO), λEtOHmax. 240 mμ (log ε 4.19); forming in concentrated H2SO4 a yellow solution which fluoresced green on a black background. Crude XXII (275 mg.) in 3 cc. C6H6 oxidized with 300 mg. OsO4 and the crude product acetylated and worked up in the usual manner gave 68 mg. 3β,11α,21-triacetoxy-17-hydroxy-20-pregnanone, needles, m. 220-5°, [α]20D 29.7 ± 2° (c 1.079, Me2CO), forming in concentrated H2SO4 a yellow solution

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ACCESSION NUMBER: 1954:46277 CAPLUS
DOCUMENT NUMBER: 48:46277
ORIGINAL REFERENCE NO.: 48:8241f-i,8242a-i,8243a-i,8244a-i,8245a-i,8246a-e
TITLE: Total synthesis of **estrone** and three stereoisomers including lumiestrone
AUTHOR(S): Johnson, Wm. S.; Banerjee, D. K.; Schneider, Wm. P.; Gutsche, C. David; Shelberg, Wesley E.; Chinn, Leland J.
CORPORATE SOURCE: Univ. of Wisconsin, Madison
SOURCE: Journal of the American Chemical Society (1952), 74, 2832-49
CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
OTHER SOURCE(S): CASREACT 48:46277

AB In an earlier publication (C.A. 42, 1948b) the key step in the total synthesis of equilenin was the condensation of 2-cyano-1-oxo-7-methoxy-2-methyl-1,2,3,4-tetrahydrophenanthrene with (CH2CO2Me)2 (I) or (CH2CO2Et)2 (II) to produce directly a substance containing the steroid nucleus. Thus, to synthesize **estrone** an attempt was made to apply this scheme. 1-Oxo-2-cyano-2-methyl-7-methoxy-1,2,3,4,9,10,11,12-octahydrophenanthrene (III) and 1-oxo-2-cyano-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene (IV) were prepared; however they failed to condense with I or II in the desired manner. Instead, ring C was apparently opened to give acidic material. Under mild conditions III and IV were recovered largely unchanged. 1-Oxo-7-methoxy-1,2,3,4,9,10,11,12-octahydrophenanthrene (9.4 g.) was treated for 16 hrs. with 6.3 ml. HCO2Et and NaOMe (from 1.86 g. Na) in 180 ml. C6H6 to give 9.77 g. (93%) crude 1-oxo-2-hydroxymethylene-7-methoxy-1,2,3,4,9,10,11,12-octohydrophenanthrene (V), m. 134-5°. V (8.2 g.), 3.34 g. NH2OH.HCl, and 120 ml. HOAc were refluxed 10 min. to give 7.8 g. (96%) of crude 7-methoxy-3b,4,5,9b,10,11-hexahydrophenanthro[2,1 - d]-isoxazole

(VI), m. 105-10°, recrystn. raised the m. to 120.8-7.8°. VI (8.6 g.) in 120 ml. C6H6 let stand 4 hrs. at room temperature with 1.6 g. Na in 45 ml. MeOH, diluted with H2O and extracted with Et2O. The Et2O layer extracted with 5% KOH and the alkaline solution acidified to yield 7.55 g. (88%) crude 1-oxo-2-cyano-7-methoxy-1,2,3,4,9,10,11,12-octahydrophenanthrene (VII), recrystn. gave m. p. 177-80°. The alkaline-insol. fraction remaining probably contained some of the isomeric [1,2-c]isoxazole. VII (2.14 g.) in C6H6 and 0.39 Na in MeOH were treated with 20 ml. MeI. The mixture remained at room temperature for 30 min. and 10 ml. more MeI added and the solution refluxed 30 min. This treatment was repeated with 10 more ml. MeI to yield 2.03 g. crude III; when pure it m. 152.4-3.2°. The alkaline solution gave 0.13 g. acidics, m. 120-30°. 1-Oxo-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene (4.22 g.) was similarly treated with HCO2Et and NaOMe to yield 85% crude 1-oxo-2-hydroxymethylene-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene (VIII), m. 87-8°. VIII (2.89 g.) treated with NH2OH.HCl in HOAc gave 2.45 g. (86%) 7-methoxy-4,5,10,11-tetrahydrophenanthro[2,1 - d]-isoxazole (IX), recrystn. gave tan needles, m. 103-4.3°. IX (2.15 g.) in C6H6 left 24 hrs. with 2 g. Na in MeOH to give similarly 1.94 g. (90%) crude 1-oxo-2-cyano-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene (X), yellow crystals, m. 157.5-9.2°. X (1.63 g.) in C6H6 was treated with a total of 65 ml. MeI to afford 1.61 g. (94%) crude IV, yellow needles, m. 108.4-9.2°. Preliminary studies of the proposed reaction scheme were carried out in the series lacking the OMe group. Thus PhC .tplbond. CK solution (24.6 g. PhC .tplbond. CH added to a solution of 9.3 g. K in 190 ml. tert-BuOH) was added during 40 min. at 60-70° to 40 g. of decahydro-1,5-dioxonaphthalene (XI) (a mixture of cis and trans forms) in 160 ml. tert-BuOH. The mixture left at room temperature for 3 hrs. and worked up gave 16.1 g. of solids which on trituration with Et2O left 2.1 g. crude 1,5-dihydroxy-1,5-bis(phenylethynyl)-decahydronaphthalene (XII), m. 210.8-12.0°; the Et2O extract gave 12.3 g. of the α-isomer of 5-hydroxy-5-phenylethynyl-1-oxodecahydronaphthalene (XIII), colorless prisms, m. 120.4-1.0°, semicarbazone, m. 204-5° (decomposition). The mother liquors yielded 0.64 g. more of the α-isomer and 0.215 g. of the β-isomer of XIII, m. 139.8-41°; semicarbazone, m. 220-20.4° (decomposition). When 20 g. of pure trans-XI was used the major yield was the α-isomer of XIII, but some of the β-isomer was obtained by chromatography of the mother liquors. When pure cis-XI was employed some XII was 1st isolated, but the main product was the α-isomer of XIII. These isomers of XIII are probably epimeric around C-5. XII was a dicondensation product. XIII (α-isomer) (1.093 g.) in 30 ml. EtOAc reduced at atmospheric pressure and room temperature during 2 hrs. with Pd-C gave the α-isomer of 5-hydroxy-5β-phenethyl-1-oxodecahydronaphthalene (XIV), m. 169-9.4°; semicarbazone, m. 223° (decomposition). Similarly the β-isomer of XIII was reduced in 30 min. to the β-isomer of XIV as prisms, m. 132.5-3.5°. XII was similarly reduced in 1 hr. to give 1,5-dihydroxy-1,5-diphenethyldecahydronaphthalene (XV) as flat pointed rods, m. 230-2°. For preparing large quantities, the acetylenic carbinols were not separated but directly hydrogenated at 2-3 atmospheric pressure in 1.5 hrs. and the product separated by fractional crystallization into 65% of α-isomer of XIV, 10% β-isomer, and 1% XV. XIV (α-isomer) (11.05 g.) was refluxed 6 hrs. in 60 ml. of 88% HCO2H to yield 7 g. of a viscous oil,

b0.75 185°; semicarbazone, m. 210-11.5°. Similarly the β-isomer of XIV (0.257 g.) gave on treatment with HCO2H, 0.221 g. of the same oil, λmaximum 253 mμ (log E 3.92), which formed the same semicarbazone in 96% yield, λmaximum 268.5 mμ (log E 4.14). The ultraviolet absorption suggests that the double bond was in conjugation with the CO group and that the compound was 5-phenethyl-1-oxo-Δ9,10-octahydronaphthalene (XVI). The α-isomer of XIV (3 g.) in 50 ml. C6H6 was saturated at 6° with anhydrous HCl and the C6H6 distilled off as long as H2O came over. This procedure was repeated and 3.47 g. AlCl3 was added slowly at 6°. The solution allowed to come to room temperature slowly, then heated at 45° for 12 hrs., then for 4 days without stirring. Working up the product gave 1.29 g. (46%) of the α-isomer of 1-oxo-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysene (XVII) recrystn. gave plates, m. 139-40°. In a similar cyclization with HCl gas and distillation the process was carried out repeatedly until no more H2O was removed to give 35% of the α-isomer and 3% of the β-isomer of XVII. Another cyclization was carried out in which the HCl gas treatment was omitted. The solution, after the addition of AlCl3, was stirred at room temperature for 7 days, then at 47° for 4.5 days to give 39% of the α-isomer and 5% of the γ-isomer of XVII, m. 121-3.5°. The β-isomer of XIV was similarly treated with 1 g. anhydrous CaCl2, HCl gas, and AlCl3 to give 38% of the α-isomer and 6.3% of the γ-isomer of XVII. When 6.33 g. of XVI was subjected to the same cyclization process the major product was the β-isomer of XVII as crystals, m. 128-30.5°; semicarbazone, m. 55.8-7.4° (decomposition). The β-isomer was isomerized in the presence of K in tert-BuOH for 2.5 hrs. to the α-isomer of XVII. A similar experiment with the α-isomer of XVII gave starting material back. This isomerization suggests that the 2 forms are epimeric at C-12a, and that the C-D rings are cis in the α- and trans in the β-isomer. XVI (0.2276 g.) and 0.112 g. 30% Pd-C were heated at 280-300° in a Heymann type of apparatus for 1 hr. to give 63% crude 5-phenethyl-1-naphthol (XVIII), m. 105.6-6.2° (from petr. ether). The α-isomer of XVII (0.047 g.) was similarly dehydrogenated in 30 min. to give 0.024 g. 1-chrysenol (XIX), m. 281-2°; acetate, m. 235-7°. A similar experiment with 0.0444 g. of the β-isomer of XVII gave 0.0178 g. of XIX in 23 min.; the γ-isomer (0.04 g.) similarly gave 0.019 g. XIX. The oily residues remaining after separation of all forms of XVII were similarly reduced to give 20% yield of XIX. A similar cyclization of 0.455 g. of XV with dry HCl and AlCl3 gave 0.69 g. of a hydrocarbon, C26H30, m. 254-6° which undoubtedly was 4b,5,6,6a,6b,7,8,12b,13,14,14a,14b,15,16-tetradecahydrobenzo[c]picene (XX). The α-isomer of XVII (2 g.) in MeOH was treated with 0.95 g. BzH and 10 ml. 33% NaOH at reflux, then heated at 40-5° for 2 days to yield 1.929 g. (72%) 1-oxo-2-benzylidene-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysene (XXI), m. 156-9.5° (pure, m. 159.3-60°), λmaximum 285 mμ (log E 4.25). The methoxy series were then studied. The Grignard reagent prepared from 50 g. m-MeOC6H4CH2CH2Br and 6 g. Mg in Et2O was added dropwise during 4 hrs. to a solution of 26 g. XI (mixture of isomers) in C6H6, the mixture stirred for 30 min. at room temperature, then 2 hrs. at 60°, and the crude reaction product dehydrated at 175° for 1 hr. with 75 g. KHSO4 gave a mixture of XI, m-ethylanisole, 1,4-bis(m-methoxyphenyl)butane, and a mixture of monosubstituted condensation products from which was obtained a semicarbazone, m. 200° [isomeric with the semicarbazone of XVI, but showed a weaker absorption (log E 3.76) at 271.5 mμ; hydrolysis yielded a ketone, C19H24O2, λmaximum 254 mμ (log E 3.58), b0.4 180°]. m-HOC6H4Ac (102 g.) was methylated with 369 ml. 15% KOH and 142 g. Me2SO4 at 60-5° to yield 94 g. (84%) m-MeOC6H4Ac (XXII), b16 130-2°. XXII (175.1 g.) in C6H6 let stand overnight with 250 g. PCl5 and the residue refluxed 10 hrs. with 225 g.

KOH in 280 ml. EtOH gave 74.2 g. (48%) m-MeOC6H4C .tplbond. CH (XXIII), after purification, b13 85°, n25D 1.5560. XXIII (3.4 g.) was treated with K in tert-BuOH and added to a refluxing solution of 4.15 g. trans-XI in tert-BuOH and refluxed for 1.5 hrs., let stand at room temperature for 12 hrs., hydrolyzed to give 50-73% of 5-hydroxy-5-(m-methoxyphenylethynyl)-1-oxodecahydronaphthalene (XXIV). Crystallization gave the α-isomer as plates, m. 83.8-4.8°; semicarbazone, m. 204.2-5.6° (decomposition). The β-isomer of XXIV was obtained from the mother liquors from the α-isomer as prisms, m. 116-16.6°; semicarbazone, m. 209-10° (decomposition). The mother liquors yielded 1,5-dihydroxy-1,5-bis(m-methoxyphenylethynyl)decahydronaphthalene (XXV), m. 188.4-9.4°. The remaining Et2O soluble material (2 g.) was the higher melting modification of the α-isomer of XXIV, m. 99.4-100.2°. The lower melting form when seeded with the higher m. form gives only the higher m. form. A similar condensation carried out with cis-XI gave largely the 99-100° form of the α-isomer of XXIV and a small amount of XXV. A similar condensation carried out on 16.6 g. of mixed isomers of XI gave 0.911 g. XXV, and 7.1 g. of the α-isomer and 0.265 g. of the β-isomer of XXIV. The α-isomer of XXIV (0.288 g.) in EtOAc was hydrogenated at atmospheric pressure and room temperature over 0.103 g. Pd-C in 19 min. to yield 0.27 g. (92%) α-isomer of 5-hydroxy-5-(m-methoxyphenethyl)-1-oxodecahydronaphthalene (XXVI), m. 76.8-7.6°; semicarbazone, m. 208.4-9.2°. The β-isomer of XXVI was similarly prepared in 91% yield by hydrogenation in 30 min., m. 89.4-91°; semicarbazone, m. 188.4-90.4° (decomposition). XXV was also reduced to 1,5-dihydroxy-1,5-bis(m-methoxyphenethyl)decahydronaphthalene (XXVII), m. 197.8-8.1°. The α-isomer of XXVI (0.176 g.) in 5 ml. HCO2H was refluxed for 3.5 hrs. to give 5-(m-methoxyphenethyl)-1-oxo-Δ9(10)-octahydronaphthalene (XXVIII) as a colorless oil, b0.4 200-15°; semicarbazone, m. 190.8-3.0°. The crude mixture of XXIV obtained from 95 g. of mixed XI was refluxed 1 hr. in 450 ml. EtOAc and 9 g. Raney Ni. The catalyst was filtered off and the solution hydrogenated in a low pressure shaker with Pd-C as catalyst. The resulting product was treated with HCO2H at reflux for 19 hrs. to afford 104.79 g. of XXVIII, n25D 1.5663, λmaximum 227.5 mμ (log E 4.04); semicarbazone, λmaximum 269 mμ (log E 4.52). In another experiment 70% XXVIII was obtained from XI. XXVIII (20.2 g.) was treated with HCl gas and AlCl3 essentially the same as described in the preparation of XVII to yield 0.6 g. of the α-isomer of 1-oxo-8-methoxy-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysene (XXIX), m. 168.4-70°; semicarbazone, m. 237-7.5° (decomposition); 2,4-dinitrophenylhydrazone, m. 210.4-11° (decomposition). The mother liquors from the α-isomer yielded the β-isomer of XXIX, m. 153.4-4.8° (depressed to 134-50° on admixt. with the α-isomer); semicarbazone, m. 267-9° (decomposition). The filtrate yielded the γ-isomer, m. 164-6.2°. After sublimation at 150°/0.05 mm. the γ-isomer was obtained as small crystals, m. 167.8-9.8°. The total yield of crude XXIX was 25% and about 90% of this was separated into the 3 forms roughly in the proportion 2:1:1. In another experiment the yields of the α-, β-, and γ-isomers of XXIX were 15, 3, and 2%, resp. The α-isomer of XXVI (0.484 g.) in C6H6 was treated with 0.650 g. AlCl3 at 40-5° for 44 hrs. After hydrolysis, the crude product was isolated as described above to give 0.129 g. (28.5%) of the α-isomer of XXIX. The β-isomer of XXVI was similarly converted to the same isomer in a 40% yield. The crude mixture of XXVI from the hydrogenation of XXIV was similarly treated to give an over-all yield of 25% from XI. The residue was distilled and the material converted to a semicarbazone, m. 187-93°, which was digested with

refluxing EtOH. The residue (2.8 g., m. 248-50°) was hydrolyzed with (CO2H)2 and the oily ketone distilled to give 0.954 g. of crude δ-isomer of XXIX, recrystn. gave a m. p. of 112-13.4°. The α-isomer of XXIX (0.42 g.) and 0.42 g. of 5% Pd-C were heated in a Heymann apparatus for 8 min. at 250° and the residue distilled to give some starting material and a small amount of the γ-isomer of XXIX along with 0.032 g. of a product m. 267.8-71° which showed a tendency to decompose It was methylated with KOH and Me2SO4 to afford colorless plates of 1,8-dimethoxychrysene (XXX), m. 198-200.5°. When this experiment was repeated at 183° for 20 min. very little H was evolved, 43% of the starting material was recovered and about 3% of what appeared to be the γ-isomer of XXIX; the infrared spectrum indicated a slight amount of impurity. The nuclear structure of the α- and β-isomers of XXIX was confirmed by dehydrogenation expts. Thus 0.2 g. of the α-isomer of XXIX was refluxed 1 hr. with 0.04 g. LiAlH4 in Et2O and C6H6 to give 0.045 g. of the α-isomer of 1-hydroxy-8-methoxy-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysene (XXXI), m. 114.5-15.5°. A 0.157 g. sample of the crude compound was dehydrated by heating with 0.25 g. KHSO4 at 200° for 10 min. under N and the resulting crude product was dehydrogenated with 0.1 g. 30% Pd-C at 280-300° for 20 min. to give 0.091 g. (64%) of 2-methoxychrysene (XXXII), m. 249.5-50.5°. XXXII was demethylated by refluxing under N for 4 hrs. with HOAc and 48% HBr and the crude product was acetylated to 2-acetoxychrysene, m. 226-8°. The β-isomer XXIX was similarly reduced with LiAlH4 to give the β-isomer of XXXI, m. 140.3-1°. This crude β-isomer was similarly dehydrated with KHSO4 and then dehydrogenated to give 75% XXXII. The δ-isomer of XXIX was similarly reduced, dehydrated and dehydrogenated to give 8.5% XXXII. The main portion of the material was an uncrystallizable oil. The α-isomer XXIX was demethylated by heating at 210° for 40 min. with C5H5N.HCl under N to give the α-isomer of 1-oxo-8-hydroxy-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysene (XXXIII) as plates, m. 204.8-6.2°; acetate, m. 131.8-2.6°. Similarly the β-isomer XXIX gave 89% crude β-isomer of XXXIII, crystallized to plates, m. 271.2-2.6°; acetate, m. 134.1-7.2°. The α-isomer of XXXIII showed no estrogenic activity at 100 μg. whereas the β-isomer showed about 10% response at this level. The α-isomer of XXIX (1.03 g.) and 0.65 g. piperonal in EtOH were heated to boiling, 6 ml. 31% KOH solution added, and the mixture left at 42° for 4 days to give 0.8 g. (53%) 1-oxo-2-piperonylidene-8-methoxy-1,2,3,4,4a,4b,5,6,10b, 11,12,12a-dodecahydrochrysene (XXXIV), m. 190.2-2.0° as the α-isomer. The β-isomer of XXXIV was prepared in 45% yield in the same manner, m. 209-11.4°. This isomer was also obtained in 40% yield from the γ-isomer of XXIX. The β-isomer of XXIX (0.1405 g.) in C6H6, 0.05 g. K in 10 ml. tert-BuOH, and 4 ml. MeI let stand at room temperature for 12 hrs., refluxed 1.5 hrs., and the cycle repeated yielded only 9 mg. of yellow crystals, m. 191.6-3°. In another experiment a compound (XXXV), m. 155°, was obtained not by methylation but by an alkaline-catalyzed isomerization. XXXV was also obtained by treating the β-isomer of XXXIV with KOCMe3. XXXV in Me2CO was oxidized by KMnO4 at 3° and the acidic material was treated with CH2N2 to afford the di-Me ester of β-isomer of 2-carboxy-7-methoxy-1,2,3,4,9,10,11,12-octahydro-1-phenanthrenepropionic acid (XXXVI), m. 110-11°. In another experiment the free XXXVI was obtained, m. 220.5-2.0°. The α-isomer of XXIX in C6H6 left at room temperature with NaOMe and 36 ml. HCO2Et for 40 hrs. gave 83% yield of 1-oxo-2-hydroxymethylene-8-methoxy-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysene (XXXVII), purified as rods, m. 160.2-1.4°. XXXVII (0.2 g.) was oxidized in Me2CO with KMnO4 to give 39% crude α-isomer of XXXVI, distillation and recrystn. gave the pure compound as

prisms or rhombs, m. 240-1.5° (decomposition). The α-isomer of XXIX (6 g.) in refluxing 600 ml. EtOH was treated with 2.8 g. BzH and 60 ml. 33% NaOH, then kept at 40-5° for 3 days and 1 day at room temperature under N to give 5.81 g. (74%) 1-oxo-2-benzylidene-8-methoxy-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysene (XXXVIII) as the α-isomer, which when pure m. 175-6.5°, λmaximum 221 (log E 4.39), 283 mμ (4.43) and λmin. 216 (4.38) and 242 mμ (3.85).

In a similar experiment the α-isomer of XXXVIII was obtained in 51% yield and a second product in 14% yield as prisms, m. 165.2-6°, λmaximum 220 (log E 4.29), 285 mμ (4.20) and λmin. 214 (4.21) and 245 mμ (3.04). The α-isomer (m. 176°) was isomerized into the 166° isomer by leaving with a KOCMe3 solution for 2 hrs. at 55°. This was probably due to cis-trans isomerization of the benzylidene group. The β-isomer of XXIX (2.585 g.) in MeOH was similarly treated with BzH and NaOH to give after 2 days at 40° a 68% yield of the β-isomer of XXXVIII, m. 152-3.1°, λmaximum 219 (log E 4.28), 285 mμ (4.34), λmin. 216 (4.26) and 241 mμ (3.67). The same product was obtained in 24% yield by condensation of BzH with the γ-isomer of XXIX. The α-isomer of XXXVIII (5.99 g.), and 45 ml. MeI were added to a solution of KOCMe3 during 20 min., then stirred in an ice bath for 1 hr., a solution containing 3.5 g. K in tert-BuOH was added and 45 ml. more of MeI and the mixture stirred for 12 hrs. to give 3.48 g. (56%) of the α1-isomer of 17-benzylidene-D-homoestrone Me ether (XXXIX), m. 116.5-18.0° and 0.801 g. (13%) of the α2-isomer, m. 147-9°. Purification gave the α1-isomer, m. 117-18°, λmaximum 221 (log E 4.22), 287.5 mμ (4.32), λmin 217.5 (4.21) and 241.5 mμ (3.54). The pure α2-isomer m. 149.2-50°, λmaximum 220 (log E 4.21), 286 mμ (4.28), λmin. 217.5 (4.21) and 241 mμ (3.58). These isomers are undoubtedly epimeric at C-12a. In a similar manner the β-isomer of XXXVIII gave the 2 addnl. C-12a epimers of XXXIX. β1-isomer in 49.5% yield as colorless rods, m. 146.6-7.2°, λmaximum 220.5 (log E 4.20), 286 mμ (4.29), λmin. 215 (4.18) and 241.5 mμ (3.45) and the β2-isomer in 17% yield as prisms, m. 147-7.8°, λmaximum 218.5 (log E. 4.24), 281 mμ (4.32), λmin. 216 (4.23) and 241 mμ (3.63). From the mother liquors after separation of the β1- and β2-isomers, 3% of a 3rd substance was isolated, m. 156-7°, λmaximum 222 (log E 4.24), 287.5 (4.51), λmin. 217.5 (4.18), and 242 mμ (3.81). This was presumably formed from either the methylated or unmethylated products by cis-trans isomerization of the type noted in the preparation of XXXV. When the α-isomer XXXVIII was methylated under more vigorous conditions (refluxing a total of 1.45 hrs.) it was difficult to obtain pure products. Oxidation of the residue in Me2CO with KMnO4 gave 35% of a gummy acidic material, which on purification m. 113-13.5°, λmaximum 279 mμ (log E 3.33) and 288 mμ (3.3) and would not form an acetate or a semicarbazone. This compound had an ultraviolet absorption spectra almost similar to 1-oxo-2-benzyl-8-methoxy-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysene, m. 171-1.7°, λmaximum 279 mμ (log E 3.40) and 287.5 mμ (3.35), which was prepared by hydrogenating the α-isomer of XXXVIII over Pd-C. The α1-isomer of XXXIX (0.2 g.) in 5 ml. each EtOAc and HOAc was ozonized at freezing temperature Three such reaction mixts. were combined and let stand overnight with 4.5 ml. H2O and 1.5 ml. 30% H2O2 to yield 71.5% α1-isomer of homomarrianolic acid Me ester (XL), 169.8-70.5°; the α2-isomer was similarly prepared as an **amorphous** powder, m. 97-120°, in a 79% yield. The β1-and β2-isomers of XL were similarly prepared The β1-isomer, 75% yield, m. 191.2-2.0°

and the β2-isomer, 77% yield, m. 225.2-7.5°. d-**Estrone** (5 g.) in MeOH and 70 ml. 17% KOH solution was added slowly to Me2SO4 during 2.5 hrs. at 25-30° (the solution was kept alkaline by adding further lots of the alkali to it, about 100 ml. in all) to yield 5.26 g. d-**estrone** Me ether, m. 162.4-6.8°, which was left overnight at room temperature with NaOMe (from 2 g. Na), C6H6 and 22 ml. HCO2Et to afford 95% crude hydroxymethylene derivative, m. 161.4-4.2°; this in HOAc was shaken at room temperature for 48 hrs. with 2 g. NH2OH.HCl to give 5.19 g. of material, m. 187-92°, which on crystallization from EtOH gave 2 forms, m. 183-4° and 202-4° (analysis indicated an oxime). This crude oxime (5.19 g.) was refluxed 41 hrs. with 5% KOH and 1.3 g. NH2OH.HCl to give 4.68 g. (85%) crude d-homomarrianolic acid Me ester, m. 253-4°, mixed m.p. with the β2-isomer of XL 225-42°. The α1-isomer of XL (0.441 g.) was pyrolyzed with 0.5 g. PbCO3 at 305°/0.05 mm. to give 0.205 g. (57%) of the α1-isomer of **estrone** Me ether (XLI) which when pure m. 115-16.2°; 2,4-dinitrophenylhydrazone, m. 273-4° (decomposition). The α2-**isomer** of **XL** was similarly pyrolyzed to give 48% of the α 2-isomer **of** XLI, **m. 67** -8.3°; 2,**4**-dinitrophenylhydrazone, m. **209** -10° (decomposition). A similar pyrolysis of the β1-isomer of XL with PbCO3 gave 81% of the β1-isomer of XLI (dl-lumiestrone Me ether) as plates m. 109-10°; 2,4-dinitrophenylhydrazone, orange prisms, m. 210-11° (decomposition). Pyrolysis of the β2-isomer of XL with PbCO3 gave 46% of the β2-isomer of XLI (dl-estrone Me ether), rods, 143.2-4°. The α1-Me ether of XLI was heated at 210° for 40 min. under N with C5H5N.HCl to give 90% α1-estrone, m. 180.6-1.4°; benzoate, m. 149-51°. The α2-isomer of XLI was similarly demethylated to give 84% α2-estrone, plates, m. 197-8.1°; benzoate, m. 159.5-61.5°. The β1-isomer of XLI (0.086 g.) was also demethylated to give 0.081 g. β1-estrone (dl-lumiestrone), colorless prisms, m. 238.5-40°; benzoate, m. 157.5-8.5°. The β2-Me ether (0.0153 g.) was demethylated to give 0.008 g. β2-estrone (dl-estrone) (XLII), rods, m. 252.8-4.7°; benzoate, m. 184.5-90°. XLII (13 mg.) and l-menthoxyacetyl chloride (2 drops) in dioxane and C5H5N gave the l-menthoxyacetate, m. 132-5°; a mixed m.p. with authentic d-estrone l-menthoxyacetate gave no depression. The irradiation of estrone was carried out by a modification of the method of Butenandt (C.A. 36, 4828.3). Thus 1.08 g. d-estrone in dioxane was irradiated for 24 hrs. to give 0.269 g. (25%) lumiestrone, m. 266-7°, [α]25D -41 ± 2° (dioxane); Me ether, m. 130-30.6°, [α]32D -27° (CHCl3); mixed m.p. with the β1-Me ether of XLI, 106-30°. The relationship of these products with those of Anner and Miescher (C.A. 45, 4260b) was discussed.

L6 ANSWER 32 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1953:9453 CAPLUS
DOCUMENT NUMBER: 47:9453
ORIGINAL REFERENCE NO.: 47:1748e-i,1749a-c
TITLE: 17α-Methyl-3,20-dioxo-Δ4-pregnene derivatives
INVENTOR(S): Plattner, Placidus A.
PATENT ASSIGNEE(S): Ciba Pharmaceutical Products, Inc.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

QAZI

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2601168		19520617	US 1950-193309	19501031

AB 3β-Acetoxy-17α-methyl-Δ5-etiocholenyl chloride (I), m. 137-40° (obtained from the 3β-HO acid by acetylation with Ac2O in pyridine and subsequent treatment with SOCl2) 1 part in dry Et2O 40 parts by volume is added to CH2N2 5 equivs. at -15° to 5°, and the mixture let stand 16 h. at room temperature and evaporated to dryness in vacuo to give crude 3β-acetoxy-17α-methyl-20-oxo-21-diazo-Δ5-pregnene (II). To II 1 part in dry Et2O 100 parts by volume is added HBr 5 equivs. in Et2O 40 parts by volume, the mixture stirred after 30 min. into H2O, extracted with Et2O, the extract washed neutral with H2O, dried, and evaporated, and the residue purified by chromatog. to give 3β-acetoxy-17α-methyl-20-oxo-21-bromo-Δ5-pregnene, m. 174-5° (from Me2CO-petr. ether). Similarly is prepared the corresponding 21-chloropregnene (III). III 1, powdered Zn 2 parts, and glacial AcOH 40 parts by volume are heated 0.5 h. at 120°, the mixture taken up in Et2O, and the Et2O layer washed with H2O and aqueous NaHCO3, dried, and evaporated to give 3β-acetoxy-17α-methyl-20-oxo-Δ5-pregnene (IV), m. 185-7° (from Et2O-petr. ether). IV 1 part in C6H6 35 and PhMe 20 parts by volume is added to cyclohexanone 5 parts by volume and (tert-BuO)3Al 1.5 part, the mixture refluxed 15 h., poured into dilute H2SO4, and the Et2O extract worked up as above to give 17α-methylprogesterone (V), m. 129-30° (from Me2CO-petr. ether). III 1 part in MeOH 40 and 10% KOH-MeOH solution 2 parts by volume are kept 12 h. at room temperature, the mixture poured into H2O, extracted with Et2O, the extract washed neutral, dried, and evaporated, and the residue purified by chromatog. to give the corresponding 3β-HO compound (VI), m. 170-2° (from MeOH). VI is converted with cyclohexanone and (tert-BuO)3Al as above to 3,20-dioxo-17α-methyl-21-chloro-Δ4-pregnene (VII), m. 165-6° (from Et2O-petr. ether). VII 1, KOAc 1, and KI 2 parts in glacial AcOH 70 parts by volume are refluxed 2 h., the mixture is stirred into H2O, extracted with Et2O, and the extract worked up as above to give V, m. 129-30° (from Et2O-petr. ether). Hydrolysis of II with 5% KOH-MeOH solution as above gives the corresponding 3β-HO compound (VIII), **amorphous** solid. VIII 1 and BzOH 1 part in C6H6 4 parts by volume heated 3 h. at 100° gives the corresponding 21-BzO compound 3-Hydroxy-17α-methyl-20-oxo-21-acetoxy-Δ5-pregnene (obtained similarly from VIII and AcOH) 1 part in PhMe 8 parts by volume heated 16 h. at 90° with (tert-BuO)3Al 1 part gives 17α-methyldeoxycorticosterone acetate, m. 163-4° (from petr. ether). I 3.5 parts in Et2O 100 parts by volume is added dropwise to an Et2O solution of Me2Cd (obtained from Mg shavings 7.6, MeBr 30, and CdCl2 28 parts in Et2O 100 parts by volume), the mixture refluxed 1 h. with stirring, carefully mixed with dilute AcOH, extracted with Et2O, the Et2O layer washed with H2O and aqueous NaHCO3, dried, and evaporated, the residue added to KOH 3.0 parts in MeOH 50 parts by volume, the mixture let stand 12 h. at 20°, diluted with H2O, and extracted with Et2O, and the extract worked up in the usual manner to give 3β-hydroxy-17α-methyl-20-oxo-Δ5-pregnene 2.1 parts, m. 180-2° (from Me2CO), oxidized by (tert-BuO)3 Al and cyclohexanone as above to V 1.3 parts. V has a progestative action on the **estrone**-pretreated mucous membrane of the rabbit uterus which is greater than that of the natural corpus luteum hormone.

L6 ANSWER 33 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN

QAZI

ACCESSION NUMBER: 1952:8765 CAPLUS
DOCUMENT NUMBER: 46:8765
ORIGINAL REFERENCE NO.: 46:1598e-g
TITLE: Aminomethyl keto steroids
INVENTOR(S): Julian, Percy L.; Meyer, Edwin W.; Printy, Helen C.
PATENT ASSIGNEE(S): Glidden Co.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2562194		19510731	US 1947-749886	19470522

AB Keto steroids are converted to their α-aminomethyl derivs. by treatment with HCHO and a nontertiary amine (Mannich reaction) (cf. C.A. 43, 1429c). Thus were prepared 16-(methylaminomethyl)dehydroisoandrosterone, m. 133-40° (decomposition); 21-dimethylaminomethyl-5-pregnen-3-ol-20-one, m. 125-31° (decomposition) (prisms from Et2O-petr. ether); 16-(dimethylaminomethyl)etioallocholan-3-ol-17-one, m. 148-50° (decomposition) (from Et2O-petr. ether); 16-(dimethylaminomethyl) **estrone**, m. 125-8° (decomposition) (from petr. ether); 16-(dimethylaminomethyl)dehydroisoandrosterone acetate, m. 128-32° (from Et2O-petr. ether). Progesterone and testosterone with (HCHO)3 and HNMe2.HCl each gave an **amorphous** product soluble in dilute HCl.

L6 ANSWER 34 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1951:22281 CAPLUS
DOCUMENT NUMBER: 45:22281
ORIGINAL REFERENCE NO.: 45:3931f-i
TITLE: Water-soluble estrogenic hormone substance
INVENTOR(S): Cook, Arthur S.; Grant, Gordon A.
PATENT ASSIGNEE(S): Ayerst-McKenna & Harrison Ltd.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
GB 645414		19501101	GB 1947-29779	19471108
FR 1310451			FR	
US 2429398		19471021	US 1944-536960	19440523
US 2551205		19510501	US 1947-777370	19471001

AB Water-soluble estrogenic hormones (I) are made by extracting an acidified urinary concentrate with a water-immiscible organic solvent and neutralizing the aqueous fraction. To urine freshly obtained from pregnant mares, preserved with an alc.-CHCl3 mixture, activated C is added with stirring at 15-30° to adsorb I. C is filtered off and resuspended in about 90% pyridine solution The pyridine solution is concentrated in vacuo at 40-50°. The concentrate is acidified to pH 4 with 15% H2SO4 and extracted with ethylene dichloride. At pH 6.9 it is extracted with ether, evaporated quickly to dryness in vacuo at room temperature to avoid hydrolysis. The residue is dissolved in MeOH, poured into acetone, filtered, concentrated in vacuo, poured into ether, the precipitate filtered off and dried in vacuo. I thus obtained is equivalent in activity to 20.5% sodium **estrone** sulfate; it is suitable for

oral administration to alleviate the menopausal syndrome in humans and causes vaginal cornification in ovariectomized adult rats. I is an **amorphous** powder, insol. in water-immiscible organic solvents, soluble in water, alc., acetone, pyridine and MeOH. It is stable as a dry powder or in aqueous solns. at room temperature against auto-hydrolysis. I is free from objectionable odor, taste and is nontoxic.

L6 ANSWER 35 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1951:21903 CAPLUS
DOCUMENT NUMBER: 45:21903
ORIGINAL REFERENCE NO.: 45:3878e-g
TITLE: Aralkylammonium steroid sulfates
INVENTOR(S): Grant, Gordon A.; Glen, Wm. L.; Barber, Richard J.
PATENT ASSIGNEE(S): Ayerst, McKenna, & Harrison, Ltd.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2534121		19501212	US 1950-163098	19500519

AB Salts prepared from steroid monosulfates and PhCH2CH(NH2)Me (I) posess central stimulating effects and are useful in estrogen therapy. Addition of I sulfate 0.23 g. in 5 ml. distilled H2O to Na **estrone** sulfate 0.39 in 6 H2O gave an immediate precipitate of I **estrone** sulfate (II). Extraction of the chilled reaction mixture with CHCl3 and removal of solvent at 35° gave, after vacuum-drying over P2O5, **amorphous** white II, m. 86-8°, containing 54% **estrone** by the Marrian-Kober test. The N-Me derivative of II, an amorph. white powder, was similarly prepared with PhCH2CH(NHMe)Me sulfate in place of I sulfate. Addnl. 1-phenylpropyl-2-ammonium sulfates prepared were: equilenin, equilin, m. 80-95°, trans-dehydroisoandrosterone, pregnenolone, and estradiol.

L6 ANSWER 36 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1950:38175 CAPLUS
DOCUMENT NUMBER: 44:38175
ORIGINAL REFERENCE NO.: 44:7337g-i,7338a-g
TITLE: Synthesis of **estrone** from androstadienedione
AUTHOR(S): Hershberg, E. B.; Rubin, Martin; Schwenk, Erwin
CORPORATE SOURCE: Schering Corp., Bloomfield, NJ
SOURCE: Journal of Organic Chemistry (1950), 15, 292-300
CODEN: JOCEAH; ISSN: 0022-3263
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
GI For diagram(s), see printed CA Issue.
AB By aromatization according to Inhoffen (C.A. 31, 4984.4) of ring A of the appropriate sterol derivative it should be possible to obtain either **estrone** (I) (Ia, R = H, R' = O) or estradiol (II) (Ia, R = H, R' = H(OH)). Saturating 12 g. dehydroepiandrosterone (III) in CHCl3 cooled in CO2-Me2CO with HCl gives 5.5 g. 5-chloroandrostan-3-ol-17-one (IV), m. 171.5-2.5°, [α]D 62.4°. Chromatographic fractionation of the residue of the CHCl3 mother liquor gives 3-chloro-Δ5-androsten-17-one, m. 155.5-6.5°, [α]D 13.5° (eluted with ether), and III, m. 145.5-7.5°. To 2.38 g. IV in 15 cc. (CH2Cl)2 and 20 cc. AcOH at 20° there is added dropwise over a period of 0.5 hr. 0.54 g. CrO3 in 1 cc. H2O and 30 cc. AcOH with shaking, the mixture is kept 2.5 hrs., 25 cc. H2O is slowly added, the (CH2Cl)2 evaporated in vacuo at 20°, and more H2O added, giving 92%

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5-chloro-3,17-androstanedione (V), m. 102-4° (gas evolution), resolidifying and remelting at 155-66°. The initial decomposition point depends upon the temperature of immersion. V, recrystd. from cold $CHCl_3$ and petr. ether, m. 99-102°, solidifies, and remelts at 160-7° (Δ4-androstene-3,17-dione) (cf. Fujii and Matsukawa, C.A. 31, 1033.8). Dropwise addition of 0.44 g. Br in 15 cc. $CHCl_3$ to 0.83 g. V in 10 cc. $CHCl_3$, concentrating the solution, adding 3 cc. 2,4,6-collidine (VI), evaporating the $CHCl_3$, refluxing the mixture 1 hr., extracting it with ether, and evaporating the ether solution after washing it with dilute H_2SO_4 and Na_2CO_3 give a mixture of approx. equal parts of Δ1,4- (VII) and Δ4,6-androstadiene-3,17-dione as shown by the absorption spectra (λmaximum 231 mμ, ε 8700, and λmaximum 269 mμ, ε 10,300, resp.). In an attempt to aid the debromination by the addition of NaI, 3 g. 2,4-dibromo-3,17-androstanedione is heated 1 hr. with 4 g. NaI in 15 cc. VI and 1.5 cc. BuOH, and the mixture dissolved in ether, washed, extracted with H_2SO_4, dried, and evaporated, giving 1.8-2 g. of a crystalline mixture (VIII), m. 156-68°. VIII (8.15 g.) is chromatographed, giving 0.71 g. 3,17-androstanedione, flat blades, m. 133.3-3.9°, eluted with petr. ether, and 0.49 g. Δ4-androstene-3,17-dione, cream-colored prisms, m. 170-1.4°. Pyrolysis of two 5-g. portions of VII according to I (C.A. 36, 5618g) but 15-20 min. at 340-50°, dissolving the residue in Me_2CO, and extracting with ether give 2.5 g. **amorphous** product which, benzoylated with BzCl-C_5H_5N 3 hrs. at 70° and purified chromatographically, gives 0.75 g. of a mixture from which, on rechromatographing, are isolated 0.26 g. **estrone** benzoate, thick prisms, m. 218.5-22°, [α]546 131.4°, [α]589, 111.3°, [α]643 80.6° (c 14.42 mg./cc., dioxane), and 40 mg. 1-methylestrone, pearly leaflets, m. 236-8.5°, [α]546 213.8°, [α]589 180.3°, [α]643 142° (c 5.94 mg./cc., dioxane). Debromination of 2,4-dibromo-3,17-androstanedione with VI gives VII, square prisms, m. 140.9-2.1°, [α]D 103.4°. VII (6 g.) in 300 cc. mineral oil (b. 310-405°) is dropped over a period of 0.5 hr. into a glass tube 1.25 in. in diameter and 12 in. long which is filled with glass beads and heated at 525-35°, the condensate diluted with ether, extracted with 5% NaOH, and the aqueous extract acidified with dilute HCl, giving 21% I, prisms, m. 256-60°, [α]D 160-2°. On repeated crystallization of I from MeOH and from Me_2CO, I m. 257.8-60.6° (cf. Kofler and Hauschild, C.A. 28, 4461.8), [α]546 199.6° ± 1.6°, [α]589 162.9° ± 0.9°, [α]D 163.5° ± 0.7°, [α]643 126.4° ± 0.8°. The synthetic I has the same biol. activity as the natural I; its benzoate, acetate, and semicarbazone also are identical with the corresponding derivs. of the natural I.

L6 ANSWER 37 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER:	1950:30195 CAPLUS
DOCUMENT NUMBER:	44:30195
ORIGINAL REFERENCE NO.:	44:5890b-h
TITLE:	Steroids and sex hormones. CLXV. The synthesis of 14-allo-17-epitestosterone
AUTHOR(S):	Heusser, H.; Eichenberger, K.; Kulkarni, A. B.
CORPORATE SOURCE:	Eidg. Tech. Hochschule, Zurich, Switz.
SOURCE:	Helvetica Chimica Acta (1949), 32, 2145-51 CODEN: HCACAV; ISSN: 0018-019X
DOCUMENT TYPE:	Journal
LANGUAGE:	German

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AB cf. C.A. 44, 2002g. Norprogesterone (I) has the constitution of a 14-allo-17-iso steroid (cf. Ehrenstein, C.A. 39, 305.8; Reichstein, C.A. 42, 5039a). Progesterone (II) differs from the natural hormones not only in the configuration at C atoms 14 and 17 but also in that II has a H atom in lieu of the Me group at C atom 10. Whereas the configuration at the C atoms 14 and 17 in I can be considered to be definitely established, that at C atom 10 is still unknown. I possesses activity similar to that of II and the question arises as to whether, in general, steroid hormones of the 14-allo-17-iso series possess a biol. activity similar to that of the natural compds. 14-Allo-17-isoprogesterone (III) shows no activity in doses up to 10 mg. on a castrated rabbit pretreated with **estrone**, and the question of whether the different behavior of I and III results only from the lack of the Me group at C atom 10 or also from a different configuration at this C atom is still open to discussion. III shows an androgenic activity corresponding to 1/2 to 1/3 of that of androsterone. To study these questions further, 14-allo-17-epitestosterone (IV) is synthesized. 14-Allo-17-isopregnenolone (825 mg.) is treated in 250 cc. CCl4 2 hrs. at 18° with 20 cc. Br-CCl4 containing 418 mg. Br, the CCl4 distilled off in vacuo at 20°, the residue treated 3 weeks at 20°, with the exclusion of light, with 34.5 cc. BzO2HCHCl3 containing 125.6 mg. active O, the mixture diluted with more CHCl3, washed with FeSO4 solution, H2O, NaHCO3, and H2O, evaporated in vacuo at 20°, the residue treated at 20° overnight in 20 cc. AcOH with 4.8 cc. CrO3-AcOH containing 45.8 mg. active O, the excess CrO3 destroyed with a little MeOH, the mixture poured into H2O, the precipitate dissolved in ether, the ether solution washed with NaHCO3 and H2O, dried, evaporated, the residue heated 1.5 hrs. in 30 cc. AcOH and 30 cc. C6H6 with 1 g. Zn dust, the mixture filtered, diluted with ether, and the solution washed with H2O and NaHCO3, dried, and evaporated, giving 860 mg. **amorphous** product which is chromatographically separated into 307 mg. 14-allo-17-epitesterone acetate (V) [eluted with C6H6-petr. ether (1:4)], m. 140-1°, [α]D22 137° (c 0.925, CHCl3), λmaximum 240 mμ, log ε 4.20, and 104 mg. III [eluted with C6H6-petr. ether (1:1)], m. 104-5°, [α]D22 139° (c 0.547, CHCl3). Heating 50 mg. V 1 hr. with 5 cc. 1% KOH-MeOH on a water bath and chromatographic purification of the product give 34.1 mg. IV, needles from C6H14, m. 138-9°, [α]D 156° (c 1.255, CHCl3), which, reacetylated from Ac2O-C5H5N, gives V. A similar saponification of 191 mg. V from the mother liquors and chromatographic purification give 43.4 mg. I in addition to 60 mg. of a compound, C19H30O2, m. 122-3°, which is not yet investigated.

L6 ANSWER 38 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1949:22619 CAPLUS
DOCUMENT NUMBER: 43:22619
ORIGINAL REFERENCE NO.: 43:4269g-i,4270a-i
TITLE: dl;-Oxysparteines
AUTHOR(S): Galinovsky, F.; Kainz, G.
SOURCE: Monatshefte fuer Chemie (1947), 77, 137-45
CODEN: MOCMB7; ISSN: 0026-9247
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
OTHER SOURCE(S): CASREACT 43:22619
GI For diagram(s), see printed CA Issue.
AB The synthesis of dl-oxysparteines is described herein and involves, e.g., the condensation of 2-pyridineacetic ester with HC(OEt)3, hydrogenation of the product, followed by a saponification to the amino acid, and a ring closure to the dioxosparteine, which is then catalytically hydrogenated to dl-oxysparteine. Et and Me 2-pyridineacetate: The ester

of 2-pyridineacetic acid (I) is obtained from the anilide (II) by the rearrangement of 2-phenacylpyridine oxime (III). III, m. 118° (3 g.), in 500 cc. absolute Et2O is mechanically shaken with 3 g. PCl5 3 hrs., producing a flocculent, faint yellow precipitate The whole is cooled with water, made faintly alkaline with K2CO3, and the anilide extracted with Et2O from the solution After distilling off the Et2O, yellow crystals remain which are purified from C6H6, yielding (90%) pure colorless crystals of II, m. 134°. By passing HCl through a solution of 2.5 g. dried II in absolute alc. (Me and Et alcs., resp.), heating 3 hrs., and distilling the alc. off in vacuo, Me and Et 2-pyridineacetate distil as a light greenish yellow liquid at 120-30° (water-vacuum pump) and give crystalline picrates m. 140-1° and 136-7°, resp.; 80-85% yield. Clemo condensation of I with HC(OEt)3 (IV): I Et ester (1.6 g.) is heated 2 hrs. with 1.5 g. IV in 2.1 cc. of Ac2O, the Ac2O and the acetate ester are distilled in vacuo out of the dark red solution, and the residue is fractionally distilled under a high vacuum. First, some I is collected at 0.1 atmospheric and 90°, then at 140° a yellow liquid, and the condensation product (V, R = Et) distils over at 220-40°. V is a greenish blue solution, and is crystallized from petr. ether as yellow prisms, m. 126°; picrate, m. 216° (from alc.). Condensation of the Me ester of I is accomplished similarly. The Me ester (V, R = Me) m. 170-1°; the picrate m. 242-3°. The yield amounts to 65%. Hydrogenation of V and saponification of VI to the free acid (VII): V (0.649 g.) is hydrogenated in 20 cc. of 2% HCl using Pt (from 0.3 g. PtO) as the catalyst. The brownish yellow solution becomes colorless after the absorption of 370 cc. of H in 1 hr. at room temperature After the catalyst is filtered out, the HCl solution is evaporated, and the ester (VI) by heating 5 hrs. with 2 N HCl is fully saponified The evaporation residue, VII.HCl, is solidified by drying in a desiccator to an **amorphous**, hygroscopic mass (0.69 g.). In order to convert this salt to VII, 0.69 g. is digested with freshly prepared Ag2CO3 on a water bath, filtered, H2S introduced, the precipitate filtered, and the solution evaporated, yielding 0.61 g. white VII. Ring closure to dioxosparteine (VIII): When VII is heated under 0.1 atmospheric, water is split off on heating to 170° (air-bath temperature), and a very viscous, faintly colored oil is distilled over, finishing at 190°. To purify VIII, it is again distilled, yielding 0.49 g. in a high vacuum at 170°. Catalytic hydrogenation of V to VI: The condensation product (0.123 g.) is hydrogenated in 15 cc. glacial AcOH with Pt (from 0.06 g. PtO). At room temperature in 30 hrs. 75.1 cc. H is absorbed. The catalyst is filtered off and the glacial AcOH evaporated in vacuo, leaving a colorless oil (VI), which is heated 20 min. in a metal bath at 200° under reduced pressure. Distillation in a high vacuum (0.01 atmospheric) converts the faintly colored oil at 170° to VIII in 0.09-g. yield. Catalytic hydrogenation of dioxosparteines to dl-oxysparteine (IX): VIII (0.49 g.) is hydrogenated with Pt (from 0.25 g. PtO) in 15 cc. of 5% HCl at 32°, absorbing 89 cc. of H; by shaking 48 hrs. no addnl. H is absorbed. The catalyst is filtered out, the solution made alkaline and extracted with Et2O, and the Et2O residue crystallized and fully purified by a high vacuum distillation (165° air bath temperature) and then recrystn. from petr. ether, yielding 0.40 g. IX, m. 112°. 3-(2-Pyridyl)-4H-quinoliz-4-one (X) (C.A. numbering): The Me ester of V (0.016 g.) is heated with 2 N HCl 4 hrs. After cooling, the solution is neutralized with Na2CO3 and made alkaline with KOH. Thereby a bright yellow, flocculent precipitate

is obtained, and the water solution is shaken 3 times with Et2O. The yellow Et2O solution, strongly fluorescent, is evaporated after drying over Na2SO4, yielding a yellow oil, then converted to yellow crystals. Further purification is carried out by distillation in vacuo. At 150-60° a yellow oil distils over, which is then crystallized, yielding X, m. 111-12° (from petr. ether).

L6 ANSWER 39 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1949:10943 CAPLUS
DOCUMENT NUMBER: 43:10943
ORIGINAL REFERENCE NO.: 43:2214c-h
TITLE: The sulfonation of some polycyclic ketones
AUTHOR(S): Djerassi, Carl
SOURCE: Journal of Organic Chemistry (1948), 13, 848-58
CODEN: JOCEAH; ISSN: 0022-3263
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

AB 1-Keto-1,2,3,4-tetrahydrophenanthrene (I) in Ac2O allowed to stand at room temperature 2 hrs. with an equimol. amount of concentrated H2SO4 gave high yields of a crystalline, H2O-soluble sulfonic acid (II), partly m. 154°, solidifying 158°, darkening 187°, decomposing 194-5°. II was not an enol sulfate since 3 hrs. boiling with dilute HCl had no effect. II + CH2N2 immediately gave the Me ester (III), m. 104-5°, soluble in 5% NaOH, recoverable on acidification, showing II to be the 2-sulfonic acid of I. II + (O2N)2C6H3NHNH2 gave only the dinitrophenylhydrazine salt of II, m. 215-16°. Similarly, the pyridinium salt m. 199-201°; NH4 salt m. 268° (from MeOH). The ultraviolet spectrum of III in EtOH closely resembled that of I, indicating no appreciable departure from the keto form. When measured in NaOH solution, the maximum at 257 mμ due to the CO conjugated with an aromatic nucleus disappeared and similarities to 1-phenanthrol (IV) were noticed. Sulfonation of 1-keto-2-methyl-1,2,3,4-tetrahydrophenanthrene gave the 2-sulfonic acid as above, began m. 108°, solidified 115°, decomposed 145-7°, [α]25D 33.5° (EtOH); Me ester, m. 105-6°. Dehydrogenation of III over Pd in p-cymene gave only I and IV. With concentrated H2SO4, isoandrosterone acetate (V) easily formed the 16-sulfonic acid (keto = 17), m. 169-72°; Me ester, m. 189-190°, [α]25D 53.3° (Me2CO); pyridinium salt, m. 246-8°, [α]25D 32.3° (EtOH). Oxidation of the sulfonation product of V by CrO3 gave 3(β)acetoxyalloetiobilianic acid, m. 229-32°, [α]25D -10.3° (Me2CO). The C-3 epimer, androsterone acetate, reacted in the same manner; Me ester, m. 176-8°, [α]25D 80° (Me2CO). Here again, the ultraviolet absorption spectra closely resembled those of the parent ketone. **Estrone** acetate sulfonated in Ac2O and the product methylated gave the crystalline Me ester, m. 199-200° (decomposition), [α]25D 139° (Me2CO); NH4 salt, sintered 270°, decomposed 320-3°, [α]25D 124° (EtOH). Infrared data also indicated that these compds. exist as keto forms. Using 1 mole concentrated H2SO4 in the rearrangement of 1,4-androstadiene-3,17-dione nearly the entire product was H2O-soluble and on evaporation gave an **amorphous** sulfonic acid with the ultraviolet absorption of a phenol, probably 1-methyl 16-sulfonic acid, m. 125-8°; pyridinium salt, m. 150° (decomposition); Me ester, m. 90-104°.

L6 ANSWER 40 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1941:42369 CAPLUS
DOCUMENT NUMBER: 35:42369
ORIGINAL REFERENCE NO.: 35:6596c-i

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TITLE: Conjugation of estrogens with proteins. I
AUTHOR(S): King, Laurence F.; Franks, W. R.
SOURCE: Journal of the American Chemical Society (1941), 63, 2042-5
CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

AB **Estrone** (I) forms a 2,4-dinitrophenylhydrazone, yellow, m. 278-80° (decomposition). Heating the dry K salt of I and p-FC6H4NO2 with a Cu catalyst for 4 h. at 200-10° gives 65% of **estrone** p-nitrophenyl ether (II), light yellow, m. 192-4°; at 160° about 50% of the I was recovered; with p-ClC6H4NO2 the best yield (30% semipure) was obtained at 145° and higher temps. produced tars. Reduction of II according to Thiele and Dimroth (Ann. 305, 114(1889)) gives 70% of **estrone** p-aminophenyl ether (III), m. 166.5-8.5°; picrate, lemon-yellow, m. about 160° (decomposition); III does not form a C6H3(NO2)3 complex; that the CO group at C17 is not affected by the reduction is shown by the preparation of the semicarbazone of III, m. about 295°, and the 2,4-dinitrophenylhydrazone, orange-yellow, m. 238-40° (decomposition). The Ac derivative of III m. 202-4°; it forms hydrated needles from aqueous MeOH. p-O2NC6H4OPh is reduced by SnCl2 and HCl in AcOH at 0°, giving 63% of Ph p-aminobenzyl ether (IV), m. 71-3°; picrate, yellow, m. 80.5-2.5°, which decomps. to an **amorphous** orange solid on standing a few days or on warming in organic solvents. III gives a pale greenish yellow diazo solution which couples with β-C10H7OH to a bright scarlet dye and with tyrosine to give an orange precipitate; the l-tryptophan (V) precipitate is pale yellow; casein in dilute NaOH gives 92% of the orange-yellow azo-protein, almost completely soluble in cold dilute NaOH, the pH of which can be adjusted with dilute AcOH to 8 without repptg. the protein; the bulk of the material separated at pH 4.5-5. Diazotized IV does not seem to couple with V but yields an orange azocasein which is soluble in dilute alkali, the pH of which can be adjusted to 8 without further decreasing the solubility of the product. III and COCl2 in C6H6-PhMe, boiled 0.5 h., appear to give **estrone** Ph ether p-isocyanate (**estrone** p-OCNC6H4 ether), m. 138-43° (72% yield); boiling with MeOH gives the Me carbamate, C26H27O4N, m. 210-12°; the Et carbamate, m. 163-5°. I and p-O2NC6H4CH2Br with EtONa give 68% of **estrone** p-nitrobenzyl ether, pale greenish yellow, m. 176.5-8.5° (semicarbazone, m. 273-5°); reduction in EtOH gives I; in AcOH no action occurs at 0° and at 20° I is recovered almost quant. Diethylstilbestrol (VI) gives 72.5% of 4,4'-bis(p-nitrobenzyloxy)-α,β-diethylstilbene, m. 183-5°; concentrated H2SO4-HNO3 gives a purple-red color; the NH2 derivative could not be prepared I and its Me ether react with p-O2NC6H4N2Cl in AcOH but reduction to an aminophenol could not be effected. VI and its di-Me ether coupled much less completely. Ten γ of III in olive oil produced estrus in more than 50% of the rats tested. An aqueous solution of the azocasein induced a more prolonged response in a dose of 830 γ but was inactive in 450 γ; on the basis of its I content the conjugate is about 10% as active as III.

L6 ANSWER 41 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1941:37649 CAPLUS
DOCUMENT NUMBER: 35:37649
ORIGINAL REFERENCE NO.: 35:5881b-i,5882a-i
TITLE: Synthetic estrogens of the diphenylethane series
AUTHOR(S): Bretschneider, Hermann; de Jonge-Bretschneider, Alice;

QAZI

Ajtai, Nikolaus
SOURCE: Ber. (1941), 74B, 571-88
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

AB Studies carried out some time ago (Hungarian pat. application, Dec. 24, 1938) lead, almost simultaneously with other workers (Dodds and co-workers, C. A. 33, 2201.2; v. Wessely and co-workers, C. A. 33, 4590.7) but by different methods, to the discovery of the estrogenically extremely active (p-HOC6H4CHEt)2 (I), m. 187°, and one (II) of the stereoisomeric forms, somewhat less active, of 2,3-bis(4-hydroxy-2-methylphenyl)butane. The starting point for these syntheses was the observation of Thiele (C. A. 5, 457) that (PhCH2N:)2 decomps. into (PhCH2)2 and N at relatively low temps. Phenol ketones or their derivs. are converted into the diazines, (RR'C:N)2 (R = alkyl, R' = aryl), which on catalytic hydrogenation take up, generally quite smoothly, about 4 atoms H. The resulting products, especially where R' is hydroxylated, are not very easy to handle because of their sensitivity. From the reactions of both the crude **amorphous** hydrogenation products and their unstable crystalline solvates the authors are inclined to believe that they are the tetrahydrides, (RR'CHNH)2; they are distinctly alkaline to litmus, are autoxidizable (in the form of their ethers and esters also) and react in solution with I, NH3-AgNO3 and O, with the latter especially in the presence of Cu compds. Perhaps the primarily formed hydrazo derivs. are themselves thermolabile, but among the decomposition products there are found basic substances together with the small amts. of (RR'CH)2 derivs. formed. If, however, they are subjected to oxidation until they no longer react with the oxidizing agent (I or O was generally used) there can be isolated 30-80% (based on the ketazine) of crystalline products which are assumed to be dihydrides, (RR'CHN:)2 .dblarw. RR'C:NNHCHRR', as indicated not only by their composition but also by their weakly basic character, their stability toward oxidizing agents, their hydrolytic cleavage and their thermal decomposition Whereas hydrolysis with HCl gives the N as N2H4.2HCl in good yield (absence of organic bases) and, in the ratio of about 1:1, the original ketone RCOR' and a polymer, on thermal decomposition all the N is split off in elementary form. This decomposition occurs quantitatively at temps. a little above 120°; the resulting product consists of at least 60% (based on the dihydride) of an equilibrium mixture of the 2 isomeric (dl and meso) (RR'CH)2, always, however, accompanied by products of half-mol.-weight which have not yet been identified; the latter are formed in greater amount from the free phenols than from their esters. Without isolating the intermediate azine hydrides, I was obtained by subjecting the hydrogenation product of the ketazine to the dehydrogenating action of Pd sponge but the yields were quite low because of the considerable amts. of half-mol.-weight products formed. The above series of reactions could be especially well followed with compds. whose HO groups were blocked. Thus, Foldi and Fodor (following abstract) converted the azine of p-MeOC6H4COEt through 2 simultaneously formed dihydrides, m. 77° and 58-65°, into the likewise simultaneously formed di-Me ethers (meso, m. 144°; dl, m. 55°) of I. From 4,4'-diacetoxypropiophenone azine, m. 135.5-6.5°, the present authors obtained, through a labile dihydride, m. 115-16°, of uncertain homogeneity, the meso-diacetate, m. 141°, of I. The relationships with the 2 forms (m. 187° and 128°) of I were established by acetylation or methylation, and, inversely, by saponification Likewise, a crystalline but not certainly homogeneous product obtained by oxidation of the hydrogenated azine of p-HOC6H4COEt gave in good yield, on methylation, the F. and F. dihydride m. 77°. Similar observations were made on 2,4-Me(HO)C6H3COMe and its Me ether. After certain difficulties had been overcome there was obtained a highly active estrogenic substance, m. 192° believed to be II. Its isomer (presumably dl) was certainly

present but the authors did not have an opportunity to isolate it. A 2nd method of arriving at substances of the above type is based on Busch's (C. A. 4, 1490) work on the action of EtMgBr on anisaldazine. By cautious work it was possible to isolate the F. and F. labile compound m. 77°.

Decomposition of this compound or the total ether-soluble product of the Grignard reaction again gave the 2 Me ethers, m. 144° and 55°, of I. Dodds (C. A. 33, 5132.3) carried out the same reaction but did not observe the intermediate N-containing product, and because of the different conditions under which he worked his yield was much smaller. In view of the discovery of this intermediate product, it can be stated with certainty that 2 mols. Grignard reagent, and not only 1 as believed by Busch, add at the 2 double bonds of the aldazine or its derivative Many attempts were made to correlate the compds. of type I with the corresponding highly active (PhCH:)2 derivs., the most important representative of which is diethylstilbestrol (III). It was attempted to effect this both by modifying the decomposition of the labile N-containing intermediate products and by dehydrogenation or oxidation of the I. Neither method gave the desired product but the 2nd method gave results worth recording. Pd sponge under conditions which result in the dehydrogenation of other ethane bridges (e. g., (NCC6H4CH2)2 → (NCC6H4CH:)2, Knoevenagel, Ber. 36, 2861(1903)) left the isomeric Me ethers of I almost unchanged (the free meso-I, m. 186°, under these conditions is attacked to a considerable extent but breaks down into half-mol.-weight fragments), but Pd-charcoal reacted entirely differently. It attacked both Me ethers, but whereas the 144° ether gave only 28% identifiable material (unchanged ether), 35% of the 55° ether was recovered unchanged and 42% in the form of its isomer. Hence it is possible to pass from the physiologically less active dl-forms (through their di-Me ethers) into the more valuable meso-forms. It was also of interest from the physiol. standpoint to prepare the mono-Me ether (IV) of I. This it became possible to do in 3 ways after it had been discovered that IV cannot be extracted from ether with dilute alkali but gives with more concentrated alkali a salt insol. in ether and difficultly soluble in water. The 3 methods were partial methylation, partial saponification and (of little importance from a preparative standpoint but interesting theoretically) simultaneous decomposition of a mixture of p-hydroxy- and p-methoxypropiophenone azine hydrides. IV, m. 120-1°, b0.001 140-50° (bath temperature), is very easily soluble in ether and MeOH, difficultly in water, gives no color with alc. FeCl3; propionate, m. 85-7°, b0.001 140-60° (air bath). Below are the results, resp., of Allen and Doisy tests on mice and on rats and of vesicular gland-growth tests on infantile rats. The values given for the A. and D. tests are the min. amts. (in γ) in 0.3 cc. olive oil which, administered subcutaneously in three 0.1-cc. doses, gave a pos. resp[illegible] in at least 75% of the animals; the vesicular gland results are [illegible] growths (in mg.) produced by 10 daily administrations of 1 γ **Estrone** 0.1, 0.7, 11; estradiol 0.033, 0.35, 19.5; III 0[illegible] 0.15, 21.5; I 0.18, 0.15, 20.0; III propionate 0.15 propionate 0.30, 0.4, 15.0; II 0.2, 0.3, -. 4-H[illegible] methylacetophenone azine, m. 251-3°; diacetate, II, m. 191-2°; dipropionate, bvac. 210°, m. 123- diacetate, m. 164°; di-Me ether, m. 137-9° prepar methylating II with Me2SO4 in NaOH-MeOH or from 4- methylacetophenone azine, m. 110-11°.

L6 ANSWER 42 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1939:54217 CAPLUS

QAZI

DOCUMENT NUMBER: 33:54217
ORIGINAL REFERENCE NO.: 33:7813c-f
TITLE: **Estrone** sulfate, a physiological excretory product from follicular hormone
AUTHOR(S): Butenandt, Adolf; Hofstetter, Heinrich
SOURCE: Z. physiol. Chem. (1939), 259, 222-34
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB Treatment of **estrone** in a mixture of dry C5H5N and CHCl3 with ClSO3H at 20° for 1 day gave estronesulfuric acid (I) the Na salt (II) of which contains 1 mole of H2O, m. 228-30° (with decomposition to **estrone** and NaHSO4) [α]D20, 110°. The decomposition also occurs on short warming in organic solvents and in H2O, especially in acid solution It is split by phenolsulfatase from Aspergillus oryzae and its ultraviolet absorption is similar to that of **estrone** acetate, known to be a phenolic ester. The C5H5N salt of I (III) m. 173-5°, [α]D20 84.1°. The Ba salt (IV) is **amorphous** and soluble in BuOH. The alkaloid salts are stable compared to other salts. Quinine salt, m. 168-70°, quinidine salt, containing 3H2O, m. 167-70°. Semicarbazone of II, decompose 258-60°; of IV, decompose above 270°. The physiol. activity of II is only 2% of that of an equal quantity of **estrone.** No evidence of protracted activity was found. III is more active than II. Treatment of **estrone** with ClSO3H in CHCl3-CCl4 gave an estronesulfuric acid, m. 210° (decomposition), giving with CH2N2 a di-Me ester, sintered at 197°, solidified and then m. 207°. Both are inactive on castrated mice. Evidence is adduced for the occurrence of I in pregnancy urine (C. A. 33, 1005.5).

L6 ANSWER 43 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1938:48168 CAPLUS
DOCUMENT NUMBER: 32:48168
ORIGINAL REFERENCE NO.: 32:6712g-i,6713a-e
TITLE: Conjugated estrogens
AUTHOR(S): Marrian, G. F.
SOURCE: Cold Spring Harbor Symposia on Quantitative Biology (1937), 5, 16-24
CODEN: CSHSAZ; ISSN: 0091-7451
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB Human pregnancy urine contains (1) **estrone** (theelin), C18H22O2, containing 3 double bonds, 1 ketonic and phenolic hydroxyl group; and (2) estriol (theelol), C18H24O3, containing 3 double bonds, 2 alc. hydroxyl and 1 phenolic hydroxyl group. Estrogens in pregnant-mare urine, all containing 1 phenolic hydroxyl group, are (1), (3) Equilin, C18H20O2, containing 4 double bonds and 1 ketonic group; (4) Equilenin C18H18O2, containing 5 double bonds and 1 ketonic group; also (5) a-Estradiol and (6) B-Estradiol, which have the formula C18H24O2 and contain 3 double bonds and 1 alc. OH group; and (7) 17-dihydroequilenin, C18H20O2, containing 5 double bonds and 1 alc. OH group. The Kober test (C. A. 25, 5908) gave good agreement with biol. tests in a series of urinary assays. The estriol values in mg. per 100 cc. of urine by biol. and colorimetric tests, were: 0.243, 0.205; 0.231, 0.240; 0.171, 0.182; 0.178, 0.178; 0.265, 0.316; 0.218, 0.306; 0.224, 0.275; 0.231, 0.280; 0.624, 0.691; 0.607, 0.700; 0.593, 0.680; 0.558, 0.705; 1.070, 1.070; 0.887, 1.200; 1.220, 0.800; and 0.989, 0.875. Similarly the **estrone** in mg. per 100 cc. of urine was 0.024, 0.033; 0.031, 0.042; 0.070, 0.071; 0.107, 0.100; 0.126, 0.127; 0.115, 0.100; 0.092, 0.100; 0.125, 0.127; 0.121, 0.123. A portion of the estrogenic material in pregnancy urines can be extracted by fat solvents only after hydrolysis with acids. Human pregnancy urines showed definite

losses under certain types of acid hydrolysis, due to oxidation. The least decomposition was observed when human pregnancy urines were adjusted to pH 1.0, then 3.3 cc. concentrated HCl per 100 cc. added and heated in the autoclave at 120° for 2 hrs. Similar cleavage may be accomplished by bacterial enzymes and by an enzyme glucuronidase extracted from mouse intestines. An **amorphous** water-insol. substance containing about 50% of estriol was isolated from human pregnancy urine; later obtained as a crystalline Na salt (I), which was shown to be a glucuronic acid combination. The combination gave a pos. Millon reaction, in alkaline solution showed a shift of absorption maximum from 2800 to 2950 A., and formed a monomethyl ether, proving that the glucuronic acid was united to estriol by a glucosidic linkage involving the terminal aldehyde group with one of the hydroxyls at 16 or 17. Following subcutaneous injections to mice, the mouse unit of estriol was 0.09 γ; of I 2.7 γ; following oral administration, 0.90 γ and 2.0 γ, resp. This was shown to be due to cleavage of I in the intestine by glucuronidase. Emmenin from the human placenta is a conjugated estriol glucuronide. The average excretion of estriol for 24 hrs. at the 8th to 9th month of pregnancy is between 20 and 25 mg. Free **estrone** and estriol amount to less than 1% of the conjugated forms. In pseudolabor and labor there is a slight fall in total estrogens and a marked rise in free estrogens. The conjugated estrogens have very slight activity as compared with the free estrogens, which appear to sensitize the uterus to the oxytocic substances, causing uterine contraction and parturition. Pregnant mare urine contains H_2SO_4 conjugates, not glucuronic acid compds. The conditions of efficient hydrolysis have not been determined for mare urine. Twenty-seven references.

L6 ANSWER 44 OF 44 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1938:908 CAPLUS
DOCUMENT NUMBER: 32:908
ORIGINAL REFERENCE NO.: 32:153b-i,154a-h
TITLE: Synthesis of substances related to the sterols. XVIII
AUTHOR(S): Peak, D. A.; Robinson, R.
SOURCE: Journal of the Chemical Society (1937) 1581-91
CODEN: JCSOA9; ISSN: 0368-1769
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

AB cf. C. A. 31, 7064.4. The condensation of the Na derivative of α-tetralone with acetylcyclohexene has already been found to yield 3 isomeric ketodecahydrochrysenes (A, B and C), of which A and B were recognized as stereoisomers (P. and R., C. A. 30, 6003.5). 2-Ketodecahydrochrysene-A(I)(2 g.), reduced in EtOAc with Pd-$SrCO_3$, gives 0.9 g. of 2-keto-1,2,3,4,5,6,7,8,13,14,15,16-dodecahydrochrysene-A(II), m. 147-8°; the semicarbazone m. 231-3°; catalytic reduction of 10.8 g. I in MeOH gives 7.3 g. II and a little of the C-isomer, m. 87-8°, separated as the oxime, m. 186-7.5°, which is soluble in cold concentrated HCl. 2-Ketodecahydrochrysene-B(III), catalytically reduced by Pd-$SrCO_3$ in MeOH (10 h., 3 atmospheric pressure) yields 2-hydroxy-1,2,3,4,5,6,7,8,13,14,15,16-dodecahydrochrysene-γ (IV), m. 155-6°, while Na in EtOH (100° for 6 h.) gives the δ-isomer (V), m. 162-3°. Oxidation of IV or V with CrO_3 in AcOH gives the B-isomer of II, m. 114-15° (oxime, m. 166-7°). III, heated with $NaNH_2$ in C_6H_6 for 6 h., gives I. Reduction of the semicarbazone of I by the Wolff-Kirschner method yields dodecahydrochrysene, m. 83-4° (previous sample not homogeneous). The K derivative of II, prepared in tert-BuOH and Et_2O, with MeI gives a small yield of the 16-Me derivative, m. 122-2.5° (oxime, m. 222-4°; semicarbazone (VI), m. 245-7°); reduction of VI yields

16-methyl-1,2,3,4,5,6,7,8,13,14,15,16-dodecahydrochrysene, m. 87-7.5°; dehydrogenation with Se at 320-30° for 20 h. gives chrysene; no reaction occurs with Pt black and the dehydrogenation with Pd-C at 300° is very slow. 6-Methoxy-α-tetralone (preparation given, 85-90% yield)(25.5 g.), transformed into the Na derivative by NaNH2 in Et2O (refluxing 7 h. in N2 atmospheric) and reacted with acetylcyclopentene (6 h.
at room temperature), gives about 10 g. of 3-keto-7-methoxy-3,9,10,11 - tetrahydro - 1,2 - cyclopentanophenanthrene-A (VII), m. 194-5° (Rapson and R, C. A. 29, 7996.1), 3.8 g. of the B-isomer, (VIII), m. 123-4°, and 0.2 g. of the C-isomer, m. 167-9° (this yield is increased by boiling the above reaction mixture for 4 h.). The absorption spectra indicate that these 3 substances are stereoisomers. Catalytic reduction of VII (Pd-SrCO3 in AcOEt) yields 3 - keto - 7 - methoxy - 3,4,9,10,11,12 - hexahydro - 1,2-cyclopentanophenanthrene-α (IX), m. 147-8°, separated as the sparingly soluble semicarbazone; the K salt (K in tert-BuOH and Et2O) with MeI gives the 2-Me derivative, m. 68-9°, with weak ketonic properties. Similarly, VIII gives the B-isomer of IX, m. 118-18.5° (dinitrophenylhydrazone, orange, m. 193-4°; 2-Me derivative, m. 75-6° (dinitrophenylhydrazone, orange, m. 171-2°; semicarbazone (X), m. 226-7°). Reduction of X with Na in EtOH (20 h. at 180°) gives 7-methoxy-2-methyl-3,4,9,10,11,12-hexahydro-1,2-cyclopentanophenanthrene (XI), b2 183°, m. 55-5.5°; X-ray data: a = 18.0 (α), b = 7.16 (β), c = 25.0 (γ), n = 8, ρ = 1.13 ± 0.03; the stereoisomeric optically active compound from the reduction of **estrone** Me ether gave a = 11.4, b = 7.15, c = 19.25, n = 4, space group P212121 (no great accuracy claimed for latter values). Dehydrogenation of XI with Se (300-320° for 5 days) gives a mixture of cyclopentenophenanthrene and a little of the 7-MeO derivative; the removal of the MeO group is a reaction which may prove within limits to be a general reaction; the reducing agent is considered to be H2Se and the essentials would appear to be Se and a hydroarom. substance at an elevated temperature 3-Keto-7-ethoxy-3,9,10,11-tetrahydro-1,2-cyclopentanophenanthrene (R. and Hawthorne, C. A. 30, 6003.8), refluxed with AlCl3 in C6H6 for 4 h., gives the 7-HO derivative, m. 249°, gives no FeCl3 reaction but soluble in dilute NaOH, from which a yellow Na salt seps. on cooling; catalytic reduction yields 7-hydroxy-3-keto-3,4,9,10,11,12 - hexahydro - 1,2 - cyclopentanophenanthrene, m. 187-9° (decomposition). The Na or K derivative of α-tetralone and β-furylisopropenyl Me ketone, mixed at -10° to -12° and then stirred 5 h. at room temperature, give 3-keto-1-furyl - 2 - Me - 1,2,3,9,10,11 - hexahydrophenanthrene, m. 137.5-8°; catalytic reduction (Pd-SrCO3 in MeOH at 3 atmospheric pressure) yields 3-hydroxy-1-furyl-2-methyl-1,2,3,4,9,10,11,12-octahydrophenanthrene, m. 140-40.5°; treatment with Br-H2O in the cold for 24 h. (to open the furyl ring) gave a heavily brominated compound, acidic but **amorphous** and all attempts to remove the Br by reduction were unsuccessful. The Na derivative of α-tetralone and Et ethylideneacetoacetate give 3-keto-1-methyl-1,2,3,9,10,11-hexahydrophenanthrene, m. 119-20°. γ-Carboxypropylideneacetone, b13 160-6°, gives a p-phenylphenacyl ester, m. 93-4°. Condensation of α-tetralone and Et γ-carbethoxypropylideneacetoacetate (XII) gave a fraction b0.8 190-200°, separated into an acid compound, C14H14O7, m. 202.5-3.5°, gives an intense FeCl3 reaction and forms a dinitrophenylhydrazone, orange, m. 205-7° and a liquid fraction yielding with Brady's reagent a red compound, C25H28O7N4, m. 183-4°, which may be an azo compound formed by addition of (O2N)2C6H3NHNH2 to the double bond of the anticipated product and oxidation No crystalline compound could
be obtained from 6-methoxy-α-tetralone and XII. AcCH2CO2Et (10 g.),

10.3 g. PhCH2CH2CHO and 15 cc. Ac2O, heated at 100° for 24 h., give 16.5 g. of Et γ-phenylpropylideneacetoacetate, b0.1 140-3°, nD15 1.5241; attempted condensation with α-tetralone gives a compound m. 130.5-1° and a mixture b1 205-45°. The synthesis of Et 2-methylcyclopentanone-3-carboxylate is described; the ester does not condense with diethylaminobutanone-MeI; the free acid, through the chloride, yields the diethylamide, b0.1 117-19° (dinitrophenylhydrazone, orange, m. 199-9.5°). 2-Chloro-6-methylheptane, b35 74-5°, nD15 1.4260, results in 16.7 g. yield from 20 g. of the alc.; the chloride forms a Grignard reagent with great difficulty and reaction with Et β-formylpropionate (XIII) gave a small fraction, b1 117-20°, which was not lactonic in character. The corresponding iodide b14 83°, nD17 1.4870; the Grignard reagent is formed smoothly but reaction with XIII did not give a lactone; 1 product is probably 2,6,7,11-tetramethyldodecane, b3 103-8°. No success was achieved in attempts to introduce the residues of MeCHBrCO2Et and ClCH2CH2CO2Et into AcCH2CO2Et. Δ1-Dihydrocitronellylideneacetic acid (XIV) (Fittig, Ann. 283, 51(1894)) is not lactonized by boiling 62% H2SO4; Et ester (XV), b10 128-31°. The Δ8-isomer of XIV is completely polymerized with concentrated H2SO4at 80°. The condensation of XV and (CO2Et)2 with K in C6H6 gives a compound which could not be distilled at 0.006 mm. and was therefore catalytically reduced, giving a product which appears to lose CO at 0.006 mm., giving a fraction b0.4 131-6° (C17H32O4?). Et dihydrocitronellate and PhMgBr give 8,8-diphenyl-2,6-dimethyl-Δ7-octene, pale yellow, b0.6 150-7°; CrO3 in AcOH yields 60% of nordihydrocitronellic acid (XVI), b10 127-9°; the chloride b8 71-1.5°; this reacts normally with the Na derivative of Et acetosuccinate but on hydrolysis of the resulting ester, no keto ester was formed and XVI was recovered; β-nordihydrocitronelloylpropionic acid was expected. A XVI containing some dihydrocitronellic acid (XVII) gave a small amount of a keto acid, b5 175-88° (semicarbazone, C14H27O3N3, m. 156-7°), derived from XVII and not from XVI.

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L11        422 L1 AND SALT

=> s l11 and sodium
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L12         95 L11 AND SODIUM

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L13          0 L11 AND PIPERATE

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        252820 AMORPHOUS
L14          1 L12 AND AMORPHOUS

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L14  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         1997:404918  CAPLUS
DOCUMENT NUMBER:          127:99741
TITLE:                    Synthesis of starch-based drug carrier for the
                          controlled release of estrone hormone
AUTHOR(S):                Won, Chee-Youb; Chu, Chin-Chang; Yu, Tarng-Jenn
CORPORATE SOURCE:         Department of Textiles and Apparel, Fiber and Polymer
                          Science Program, Cornell University, Ithaca, NY,
                          14853-4401, USA
SOURCE:                   Carbohydrate Polymers (1997), 32(3/4), 239-244
                          CODEN: CAPOD8; ISSN: 0144-8617
PUBLISHER:                Elsevier
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB    The objective of this study was to provide new synthetic route to prepare
      starch as a potential carrier for controlled release of drugs.  A starch
      was modified with bromoacetyl bromide in order to provide more reactive
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sites for coupling of bioactive **estrone** and a suitable spacer between the drug carrier and the hormone. The degree of substitution/anhydroglucose (AHG) unit was calculated from the bromine content and ranged from 0.11 to 2.29, depending on the ratio of bromoacetyl bromide to starch. The starch-**estrone** conjugate was then synthesized by reacting bromoacetylated starch with the **sodium salt** of **estrone**. The structures of bromoacetylated starch and starch-**estrone** conjugate were determined by means of FTIR, 1H NMR, 13C NMR and UV. Addnl., x-ray diffraction patterns showed the **amorphous** character of the bromoacetylated starches.